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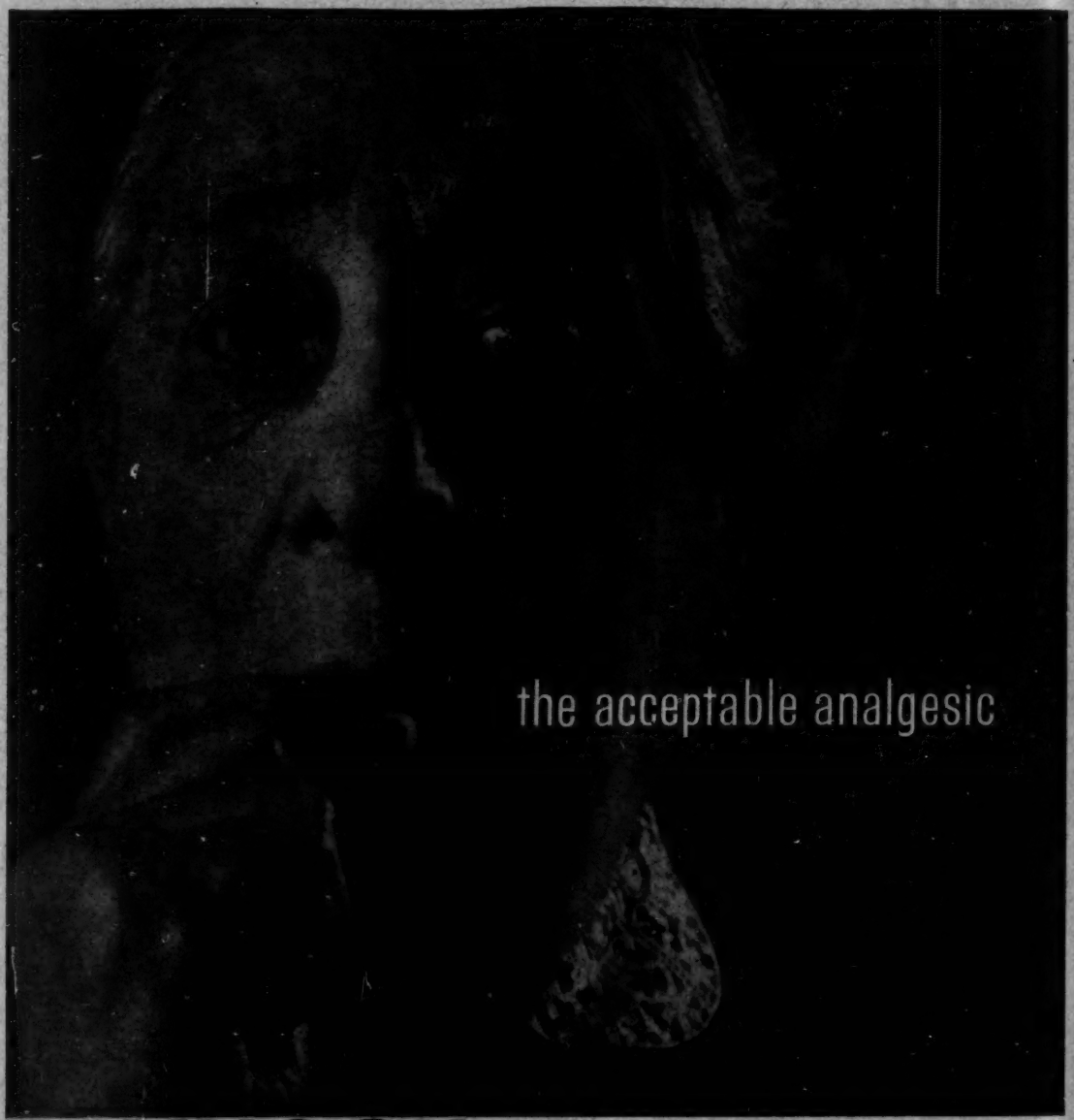

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 29 1960

CONGENITAL BILIARY ATRESIA

BY

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[WITH SPECIAL PLATE]

Congenital biliary atresia, though a relatively uncommon occurrence, still remains one of the most disappointing of neonatal surgical problems, relieved all too rarely by occasional success in treatment. Following John Thomson's original survey of 50 cases in 1891, it was not until 1916 that J. B. Holmes suggested treatment by surgical means after reviewing over 100 patients. Though the first recorded unsuccessful attempt was made by Giesel and Witze in 1895, it was not until 1927 that Ladd first performed a successful anastomosis, and up till 1952 he, and later Gross, quoted the extraordinary total of 146 babies with biliary atresia, among whom they obtained a cure in 12 cases. This does not include those children with inspissated bile in the ducts —a condition which must often spontaneously regress, even though laparotomy may be needed to diagnose it. We doubt if any series can match this either in numbers or cures; in fact, even in large children's centres in Britain such a case must rank as a rare occurrence.

Aird records having had ten cases, none of which were operable. Our own recent inquiries throughout medical centres in Great Britain, Europe, and America have revealed that not a single pathologist has come across a case in which sections of the liver before and after the relief of congenital atresia were available. Indeed, they all write quite emphatically that they had never encountered a subject thought to be suitable for operation. After the completion of this paper, however, we heard of three patients who had been successfully operated on at the Children's Hospital of Philadelphia and were followed up for five years. No post-operative material was available for study. We are indebted to Dr. Irving J. Wolman for this information.

Table Showing the Larger Published Series of Cases of Biliary Atresia

Authors	Origin of Report	No. of Cases	No. Corrected	Correctability Rate %
Donovan, 1937	New York	11	1	9
Amberg and Zuschlag, 1944	Mayo Clinic	30	4	13
Gray *et al.*, 1948	Mayo Clinic			
Leyva and Madigan, 1948	Washington Children's Hospital	18	9	50
Moore, 1953	Indiana	31	8	26
Ladd and Gross, 1953	Boston	146	27	19
Redo, 1954	New York	27	10	37

The larger published series are given in the Table, which shows the percentage correctability rate (as opposed to cure) to vary from as low as 9% to 50%, the average being 34%.

Recently at University College Hospital we have had four such patients, of whom one was successfully treated surgically, and it seemed worth while recording them, not so much for this fact alone, but as a background to the changes in the liver which are associated with biliary atresia.

Case 1

A girl first seen when 6 weeks old, jaundice having been first noticed when she was 2 weeks old. At operation a small rudimentary gall-bladder containing no lumen was found. There was no trace of any other extrahepatic biliary apparatus. The liver was dark green, finely nodular, and hard. She lived for eleven months, having to be admitted on seven occasions for abdominal paracentesis.

At necropsy the liver showed characteristic biliary cirrhosis with dilatation of the bile-passages. No major ducts could be demonstrated. There were also characteristic oesophageal varices.

Case 2 (Mr. H. R. I. Wolfe's Patient)

A boy first seen when 4 weeks old. Jaundice became apparent at 12 hours, and gradually increased without remission. At operation the gall-bladder was found to be absent, being represented by a small strand of fibrous tissue. A stenosed cystic duct joined a rather larger stenosed hepatic duct, which was thought to be the left-hand one. The common bile-duct and right hepatic duct were absent. The fibrous cord was dissected out backwards into the portal fissure and a very small fusiform dilatation was found. On cutting across this a few drops of clear bile appeared, but only a fine lacrimal probe could be introduced into the lumen of this duct.

An anastomosis was attempted between this fine duct and the duodenum. The liver was greatly enlarged, dark green, and granular. Following this the jaundice was not relieved. This child also survived eleven months, but unfortunately no necropsy was performed.

Case 3

A boy first seen when 2 weeks old. He had been what was described as "slightly yellow" from birth, and on admission was quite obviously jaundiced. A liver biopsy was done, which showed gross biliary cirrhosis with stasis in the canaliculi. There was some evidence of scattered liver regeneration and there was much glycogen storage. At

laparotomy the gall-bladder was found to be represented by a thin fibrotic cord which had a tiny empty lumen. There was no trace of any bile-ducts. He collapsed and died within 24 hours of operation. At necropsy, section of the liver did not show any macroscopic dilatation of the bile-ducts or canaliculi. The beginnings of the two main hepatic ducts were visible, but had almost microscopic lumina.

Case 4

A boy who was first seen when 7 weeks old. He had been noticed to have pale stools and dark urine for a week, and following this progressively deepening jaundice. At operation the common bile-duct was found to be atretic to a point 0.5 cm. below the portal fissure, where the dilated end was clearly visible. This was anastomosed to the first part of the duodenum. The liver was enlarged, greenish, smooth, and hard, and a piece was taken for biopsy. A normal-coloured stool was passed on the second post-operative day, and he then made an uninterrupted recovery. The jaundice faded quickly, but there was a detectable trace when he was discharged two weeks later.

He has since remained well and has developed normally. He is now nearly 4 years old, and a short while ago a further biopsy was taken from the liver for comparison with the first specimen.

Pathology of Case 4

Before Operation for Relief of Obstruction

Fairly large sections (10 × 5 mm.) from pieces of liver removed at operation well fixed in 10% neutral formol saline. Stained with Ehrlich's acid haematoxylin and eosin, Van Gieson, Gomori's reticulum method, Best's carmine after absolute alcohol fixation, and the P.A.S. method.

Sections Stained with H. and E.

Capsule.—Mostly normal in width, cellularity, and type of fibrous tissue. Here and there small flat plaques of collagen protrude, free from cells. The lining mesothelial cells are flattened and scanty. No inflammatory-cell infiltration. Scattered broad, wedge-shaped bands of cellular connective tissue pass inwards to the centre of a lobule. Blood-vessels immediately beneath the capsule are congested. There is no fibrin or fibrous adhesions.

Portal Canals.—(1) The connective tissue is increased as islands (insular) and also growing outwards (inter-insular) to join up here and there with other tracts. Inter-lobular fibrosis, however, is not complete. A few lobules show very wide bands joining together the portal tracts. From all of the fine bands small groups of collagen fibres are growing into adjacent lobules. Fibroblasts are present in all stages of active proliferation, together with a few polymorphonuclear leucocytes, eosinophils, fairly numerous lymphocytes, an occasional plasma cell, and many monocytes, all of which are healthy and free from inclusions or deposits, though many monocytes contain bile pigment. In a few tracts there are small collections of lymphocytes, but these are without a truly lymphoid pattern or germinal centres. They are found in the largest portal tracts and are often close to the portal veins. There is no necrosis, but free bile pigment is present. There is no haemorrhage and no other pigment is obvious. (2) Bile-ducts: These are increased in all portal tracts. There are signs of proliferation of the small ducts in the form of tall cuboidal epithelium containing prominent nuclei with a large chromatin network. Obvious epithelial budding is also present. There is great variation in the size of the duct nuclei, some being several times normal size and ovoid. Many cells contain free bile pigment. A few mitoses found after a prolonged search. There is no degeneration or necrosis in the bile-duct epithelium. Large and medium-sized bile-ducts are normal. There is no obvious distension anywhere. The basement membrane is difficult to see in the section stained with H. and E. The lumen of the small ducts contains bile, occasionally blood, well-formed bile thrombi, occasional lymphocytes which are single or clumped, and very rarely mucus (see P.A.S. staining). There is no obvious periductular fibrosis or cystic dilatation. Here and there small bile-ducts are growing inwards, invading lobules, but they do not go very far. Small bile-ducts are numerous within the bands that enclose some of the lobules (3) Blood-vessels: The portal vein branches are normal and not thickened, nor are they increased. There is no thrombosis, haemorrhage, hyaline degeneration, or necrosis in the walls. They are not inflamed, though the new connective tissue encroaches on them. The capillaries are not obvious, the hepatic-artery branches are normal. A few distended lymphatics are present, but they have to be looked for. They contain no leucocytes in the lumen. The centrilobular and hepatic veins are not obviously thickened. They are congested, but not necrotic or haemorrhagic.

Liver Lobules.—These seem somewhat larger than normal, but are not nodular. They are usually well defined by bands either completely or partially surrounding them. There is some intralobular fibrous tissue here and there as narrow bands. The canals of Hering can be traced into the lobules, but not very far. There is no focal, zonal, or isolated cellular necrosis. There is no haemorrhage, but some patchy sinusoidal congestion. There are no bile lakes and no definite regeneration.

Liver Cells.—These are mostly swollen, pale, and vacuolated with glycogen. There is no necrosis, and mitoses are not found. There are no giant cells. Bile pigmentation is seen as a fine stippling in many cells, with some clumps of inspissated bile here and there throughout the lobule, but there is no special distribution of these. There is no fibrosis deep in the lobules; the liver cells near the bands are shrinking.

Kupffer Cells.—These are not increased and contain no mitoses. Bile pigment is seen in many, with occasional clumps of bile. There are no proliferating groups of cells.

Bile Canaliculi.—Canalicular stasis is patchy and prominent with many bile thrombi and microliths, and there are many inspissated amorphous bile masses. The canaliculi are dilated, but not infiltrated with cells. There is no epithelial lining for the canaliculi anywhere.

Sections Stained with Van Gieson

These show a moderate amount of fuchsinophilic collagen, but less than would have been supposed from the sections stained with H. and E. Fine collagen bands penetrate the lobules at the periphery. The capsule of the liver is shown to be broader than in the H.-and-E. sections.

Reticulum-stained Sections

The reticulin is much increased everywhere, the portal tract being especially affected. Bands spreading out around the lobules are largely reticulum, and there is also much in the bile-duct walls.

Glycogen (Best's Carmine)

About one-half to two-thirds of the liver cells give deep-red staining; others remain unstained. There is none in the bile-duct epithelium. Saliva test is positive.

P.A.S. Staining

There is no increase of P.A.S. material in the portal tracts.

Three Years After Operation

The specimen consists of a small piece of liver about 4 × 2 mm. fixed in 10% formol solution.

Sections Stained with H. and E.

Capsule.—Normal, with a few spindle-shaped plaques or buttons projecting here and there. It is acellular, with no fibrin or adhesions. There are no wedge-shaped scars dipping into lobules.

Portal Canals.—(1) Connective Tissue: Normal in amount and distribution. The pattern also is almost normal. Fibroblasts are present, mostly elongated and spindle-shaped, but a few are still plump. A few scattered lymphocytes and

some tiny clumps of lymphocytes, but very few monocytes and no polymorphs, eosinophils, or plasma cells. The cellularity is just a little in excess of normal. There is no bile effusion or haemorrhage and no pigmentation of any kind. (2) Bile-ducts: Mature, mostly small and not increased. They are of normal structure, with no bile stasis or inflammation. There is certainly no evidence of proliferation or dilatation, and they are not invading the lobules. Medium and large ducts are normal. The canals of Hering are difficult to find. (3) Blood-vessels: All normal.

Liver Lobules.—Ill-defined but normal.

Liver Cells.—A moderate amount of glycogen only. No mitoses are present. There are no giant cells, no bile pigmentation, and no fibrosis or necrosis.

Kupffer Cells.—Normal. No bile stasis.

Bile Canaliculi.—Difficult to find because they are empty. No thrombi.

Other Stains

Normal results were obtained with Van Gieson and reticulum staining.

Comment

This case has much of interest for the student of regeneration in general and of liver restoration in particular. It conforms to the usual picture which is found in babies with atresia of two months' duration. At this time the liver is usually enlarged, though it may shrink with further obstruction. It is deep green, seldom irregular, and firm. It cuts with resistance, and presents a fine white or grey uniform mottling corresponding to the abnormal portal tracts. Microscopical examination shows that the capsule is seldom abnormal. The portal tracts are enlarged from hyperplasia and distension of the bile-ducts and progressive fibrosis. Periportal connective tissue is broad and may embrace lobules as interinsular and annular cirrhotic bands. Some of these penetrate the lobules to some extent, and are accompanied by proliferating bile-ducts and inflammatory cells. A few lobules are often segregated by the encroaching periportal bands; others are actively regenerating and resemble tiny adenomata.

The most constant feature is bile-duct hyperplasia and distension; when this is severe, hyperplastic ducts ring around and invade lobules. Transitions between liver-cell trabeculae and new bile-ducts are quite easily found, pseudo-ducts and solid buds of cuboidal-duct epithelium are numerous, but the medium-sized and large ducts often remain unchanged apart from distension. Bile-duct increase is not correlated with the length of obstruction, and infants dying within two to three months may show more ducts than those living for seven months or more. Occasionally small granulomata are present in the walls of large ducts that are caused by effusion of bile, but the bile lakes of extrahepatic obstruction in adults are rarely seen. Bile stasis is always prominent, both in the interlobular and perilobular bile-channels and in the intercellular canaliculi. The latter stand out very distinctively because of their distension with green inspissated bile, greenish-black thrombi, and laminated microliths. Close to these thrombi the liver cells are sometimes necrotic and bile-stained, but necrosis is seldom extensive. Binucleate liver cells are numerous and multinucleate giant cells are easy to find.

So far as we know, convincing evidence of recovery in human beings from the effects of fairly prolonged biliary obstruction has not previously been presented. A firm experimental basis has, of course, existed ever since the early work of Bell (1926) in America and that of Cameron and Oakley (1932) in Great Britain with dogs and rats. In a recent investigation of spontaneous restoration of the ligated common bile-duct in rats Cameron and Prasad (1960) show that quite severe biliary cirrhosis may completely disappear by a process of liver-cell proliferation, dedifferentiation of hyperplastic intrahepatic bile-ducts, and the formation of many new liver lobules. Fibrous tissue is incorporated in the framework of regenerating lobules, though some of it actually vanishes. There is, however, a limit to the reversible stage of biliary cirrhosis beyond which the liver does not recover when relieved from the strain of extrahepatic duct obstruction.

Embryology

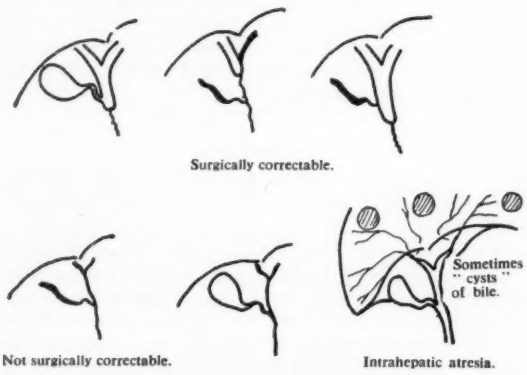
Most of the liver and its bile-vessels comes from the endoderm of the foregut as a diverticulum adjacent to the yolk-sac at the end of the fourth week of embryonic life (Cameron and Hou, 1961). Cells derived from the upper portion of this diverticulum rapidly penetrate the septum transversum as cords or cribriform sheets and become closely aligned to the vitelline veins. Some observers maintain that mesenchymal or mesothelial cells of the septum join with the endodermal component to produce new liver cells. Whether this is true or not, trabeculae of functioning liver cells are clearly recognizable at about the sixth week, and they grow vigorously during the second and third months. A lobular pattern is, however, slow in emerging. Bile canaliculi are present in large numbers by the sixth week, some time before the hepatic cells begin to secrete bile. At this time, too, the embryonic hepatic duct is sending out many branches, which join up with canaliculi attached to the liver cells. Quite a number of liver cells apparently are derived from these tiny branches.

Small bile-ducts differentiate towards the end of the second month by a kind of transformation process that involves the liver-cell trabeculae that lie near branches of the portal vein. In the 16-mm. foetus they are quite distinct, but every variety of transition between unchanged liver cells and differentiating bile-ducts may be made out. As a result of successive transformations a network of ductules emerges and spreads out round the portal vessels, from which they are separated by mesenchymal cells. In this way the portal tracts are produced, which contain new ducts of varying sizes linked to the liver-cell trabeculae and the minute canaliculi by the tiny ductules known as the canals of Hering. At 12 weeks the liver is excreting bile, haematopoiesis having begun in the sixth week and reaching its greatest activity during the fifth month. The extrahepatic bile-ducts are derived from the caudal portion of the primary diverticulum. As is usual with hollow tubes in the embryo, hyperplasia obliterates the lumen in the fourth month, but subsequent canalization restores this space by the fifth month. Anomalous bile ducts occasionally develop, leading straight into the gall-bladder, and two cases are recorded in which a duct passed from the left lobe of the liver behind the lesser omentum towards, but not communicating with, the duodenum.

Aetiology

Incomplete development of the above process can account for some cases of atresia, but does not satisfactorily explain all of them. In some instances an intrahepatic atresia occurs, sometimes associated with

extrahepatic atresia. In a few, large cyst-like spaces full of bile are found in the liver, which are probably an expression of maldevelopment of the intrahepatic biliary system. Anastomosis and drainage of these cysts has not been followed by relief of the obstruction, as it appears that they may not communicate with the rest of the biliary system and drain only a very small portion of liver substance.



Common main types of atresia. Possible permutations and combinations of these are, of course, very great.

Inflammation, congenital syphilis, and erythroblastosis have in the past been blamed without any solid foundation of proof. It seems strange that minor expressions of such maldevelopment are not more often seen in adult life causing trouble with biliary flow if an embryonic explanation is the only one, but inquiry has failed to elicit any evidence of this.

Moore feels that these anomalies arise from "gross embryonic aberration" rather than a simple arrest of development. Whitten and Adie (1952) review the histories of eight families in whom the defect appeared familial, and added the record of a further family. From one to as many as six children in one family are reported as being affected. The incidence of this abnormality appears to be about one in 25,000 to 30,000 children.

Diagnosis

Progressive jaundice in infancy may be due to several causes. Icterus neonatorum, though sometimes causing alarmingly deep colour, can usually be easily diagnosed, for the jaundice diminishes rapidly in the first 10 to 16 days, there is no liver enlargement, and the urine and stools are normal.

Erythroblastosis Foetalis

If the possibility of this occurring is unsuspected, confusion may inevitably arise, but investigation of the blood should rapidly clear up any difficulty. A positive Coombs test, the blood group of the mother, a marked anaemia with immature red cells in the baby, form a characteristic pattern. There is, however, the possibility that liver damage and blocking of the bile-ducts with inspissated bile from rapid breakdown of red cells may sometimes superimpose the picture of an obstructive jaundice on this condition, and occasionally surgical exploration and "flushing" of the bile-ducts is necessary before an atresia can definitely be ruled out. In the past many cases of inspissated bile have probably been confused with neonatal hepatitis.

Congenital Syphilis

This is fortunately becoming much rarer and is not often missed. The mother's history and a positive Wassermann reaction are usually sufficient evidence.

Neonatal Hepatitis

This group of conditions appears to be becoming more frequent and is often a great source of confusion. Its origin is obscure and its effect sometimes prolonged. The baby is said to be more ill with hepatitis and the stools are not completely without pigment. Liver-function tests are usually invoked to try and tell the difference, but frequently liver damage and obstruction are severe enough to make such tests inaccurate and confused. However, Lehmann *et al.* (1957) state that estimation of the pseudo-cholinesterase level always differentiates clearly between biliary obstruction and hepatitis, being normal in the former and low in the latter.

We think it is fair to say that surgery in treatment is not necessary in children with atresia who are seen early in life. As we have shown, liver damage is largely reversible, and a week or two spent in careful investigations and observations will not be time wasted. It is perhaps inevitable that, even so, a certain number of cases of hepatitis may be explored unnecessarily. In any case, exploration in the first week or two of life is hazardous once the first 48 hours are past, and liver damage may make it more so. A slightly older child seems better able to withstand what may be a prolonged operation.

Jaundice in biliary atresia is not necessarily progressive from birth. The first meconium is often normal. It is said to be so because it is formed at the fourth month and is usually green in colour. Following this the contents of the bowel lose their colour and the stools rapidly become putty-coloured. However, as jaundice progresses bile may be excreted in the intestinal juices, and this may frequently impart a tinge of colour to the stools, which varies a little from day to day and may be taken as an early sign of remission. The urine becomes dark before the clinical onset of jaundice, and remains so with a high bilirubin level. Strangely enough, the blood picture shows little change. The platelet count is normal, and bleeding and clotting times are not altered until late. It is usually not until the fourth to sixth months that liver damage is sufficient to impair prothrombin production with the onset of haemorrhage, even though vitamin K absorption is poor throughout, and it is wise to give it pre-operatively. In fact, it is a tragic occurrence that so many of these babies for whom nothing can be done survive for so long, sometimes for over a year, and these are said to be those in whom intrahepatic atresia is present. By this time they exhibit all the characteristics that might be expected—namely, a huge liver with large spleen, ascites, and oesophageal varices.

Treatment

In view of what has been said and written about blockage of imperfectly formed bile-ducts, we have tried as a pre-operative measure the effect of dehydrocholic acid with a fine tube so placed that it was hoped the tip lay in the duodenum. While it was obviously not successful in any of our cases, it does seem that there is a place for a trial of this sort, as it may serve to identify those babies who will improve without surgery. Ladd and Gross record two cases in which no obvious

bile-ducts were found at operation, but subsequently the jaundice cleared and the babies recovered. Otherwise the only course open is a minute examination of the anatomy from the portal fissure down to the duodenum through an adequate incision in the hope that a sufficiently dilated piece of hepatic or common duct may be discovered that can be anastomosed to the intestine. If the block is below the entry of the cystic duct and the end of the common duct is very small, the gall-bladder itself can be used, and this is of course technically much easier. If the ducts appear tiny and fibrous, it is worth trying to distend them by injecting through the gall-bladder, if it is present, either saline or methylene blue. Alternatively, diodone may be used and radiographs taken on the table. Such a procedure would obviously be that of choice in those cases with tiny ducts blocked with solid material which can be washed through.

Summary

Four cases of congenital atresia of the bile-ducts are described in which operation for relief of obstruction was attempted, with a successful outcome in one. Microscopical examination of the liver before and three years after operation in the successful case showed complete recovery, with regeneration of damaged liver regions, restoration of biliary flow, and removal of fibrous bands that had begun to grow around the liver lobules.

The clinical and pathological changes produced by congenital atresia are discussed in terms of embryology, and suggestions are put forward for a rational treatment of the condition.

We are grateful to Dr. G. R. Osborn, pathologist to the Derbyshire Royal Infirmary, for the photomicrographs.

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A recent British Standard (B.S. 3277:1960) has been prepared at the request of the Ministry of Health. It deals with tuber-bearing thigh corsets (bucket tops) made of blocked leather (sometimes called moulded leather), non-tuber-bearing thigh corsets of blocked leather, and cuff tops. It distinguishes clearly the essential differences between the three types of appliances and ensures a reasonable quality for the finished product. The standard deals primarily with materials and those details of construction that are independent of individual clinical requirements. Copies may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1, price 3s., postage extra to non-subscribers.

FOUR HAEMOGLOBINS IN ONE INDIVIDUAL

A STUDY OF THE GENETIC INTERACTION OF Hb-G AND Hb-C

BY

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[WITH SPECIAL PLATE]

Hitherto the finding of a variant of adult haemoglobin together with the normal pigment in any individual has been taken to indicate the presence of a single abnormal gene, and this hypothesis has been confirmed (except for haemoglobin H) whenever adequate family studies have been made. In those instances where two abnormal, but different, genes for haemoglobin production have been inherited one of two results has been found: either the two variants appear without haemoglobin A (as in sickle-cell–haemoglobin-C disease), in which event the genes for the variants concerned can be regarded as two allelomorphs of a normal gene, which they entirely supplant; or the two variants appear together with haemoglobin A (as found, for example, in the simultaneous occurrence of haemoglobins A, D, and K) (Cabannes and Portier, 1959), when one locus no longer suffices. The view that the difference between normal and an abnormal haemoglobin is determined by a single gene has now been clarified by the work of Hunt and Ingram (1959), who have shown that certain of the abnormal haemoglobins differ from normal adult haemoglobin in the chemical structure of only one of the two types of polypeptide chain of which the haemoglobin molecule is composed. Thus the presence of a single abnormal gene is finally seen as a chemical difference in a single polypeptide chain. Recently Itano, Singer, and Robinson (1959) have suggested that in certain circumstances an abnormal haemoglobin may be formed which differs from normal adult haemoglobin not in just one but in both polypeptide chains, and, furthermore, that when this occurs the individual would be expected to possess four major adult haemoglobins. Their argument depends on a consideration of the composition and interaction of the haemoglobin variants.

Human adult haemoglobin (Hb-A) consists of two pairs of polypeptide chains, designated the α^A and β^A chains, with a haem group attached to each chain (Rhinesmith *et al.*, 1958; Perutz *et al.*, 1960), and its molecular formula may be written $\alpha_2{}^A\beta_2{}^A$. The abnormal haemoglobin S (Hb-S) differs from Hb-A in the amino-acid composition of the β-chains, one glutamic-acid residue being replaced by a valine residue, but not in the composition of the α-chains, and thus its formula may be written $\alpha_2{}^A\beta_2{}^S$ (Ingram, 1959). Other abnormal haemoglobins have the same β-chains as Hb-A, but differ in the α-chains. For example, Murayama and Ingram (1959) have shown that in haemoglobin I (Hb-I) the α-chains are abnormal, and

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Itano and Robinson (1959) have given its composition as $\alpha_2^I\beta_2^A$. The substitution, as in Hb–S, of one amino-acid residue for another having a different charge alters the net charge on the haemoglobin molecule and as a consequence alters its rate of migration in an electric field.

At acid *p*H the haemoglobin molecule dissociates into two unlike subunits, which for Hb–A are α_2^A and β_2^A, for Hb–S α_2^A and β_2^S, and for Hb–I α_2^I and β_2^A. When the acid solution is neutralized the subunits combine to re-form the complete haemoglobin molecule. If two different haemoglobins each with a β-chain anomaly are present in the solution subjected to dissociation, then, because there is only one type of α_2 subunit available, recombination can only produce the original two haemoglobins. On the other hand, if the solution contains one haemoglobin with abnormal α-chains and a second with abnormal β-chains, two new hybrid haemoglobins may be formed (Itano *et al.*, 1959). Thus, in the case of Hb–S and Hb–I the two possible "hybrids" are the doubly abnormal haemoglobin I/S ($\alpha_2^I\beta_2^S$) and Hb–A, as illustrated by the following equation:

$$\underset{\text{Hb–S}}{2\alpha_2^A\beta_2^S} + \underset{\text{Hb–I}}{2\alpha_2^I\beta_2^A} \xrightarrow{\text{dissociation}} 2\alpha_2^A + 2\beta_2^S + 2\alpha_2^I + 2\beta_2^A$$

$$\xrightarrow{\text{recombination}} \underset{\text{Hb–S}}{\alpha_2^A\beta_2^S} + \underset{\text{Hb–A}}{\alpha_2^A\beta_2^A} + \underset{\text{Hb–I}}{\alpha_2^I\beta_2^S} + \underset{\text{Hb–I}}{\alpha_2^I\beta_2^A}$$

Thus four haemoglobin species could be produced, the doubly abnormal haemoglobin I/S being composed of the abnormal subunits of Hb–I and Hb–S.

Itano *et al.* (1959) suggest that the same series of recombinations of subunits may occur *in vivo*, and they believe this to have occurred in the family described by Smith and Torbert (1958), where Hb–S and another abnormal haemoglobin, Hopkins–2 (Hb–Ho.2), segregate independently, and in which some members show the three haemoglobins A, S, and Ho.2 by conventional electrophoretic techniques. Itano *et al.* (1959) have shown that Hb–Ho.2 has abnormal α-chains, and they have therefore postulated that in those members who show three haemoglobins the haemoglobin migrating in the position of Hb–A is actually a mixture of the doubly abnormal haemoglobin Ho.2/S ($\alpha_2^{Ho.2}\beta_2^S$) and Hb–A. The doubly abnormal haemoglobin in this instance has the same charge, and therefore the same mobility, as Hb–A, because the extra positive charges on the β_2^S subunit compared with β_2^A are balanced by the extra negative charges on the subunit $\alpha_2^{Ho.2}$. Its separate existence has not yet been demonstrated, and in this particular instance confirmation of the theory awaits the detailed chemical examination of the "Hb–A" from these cases (Itano *et al.*, 1959).

We report here a study of a family which confirms the postulate that doubly abnormal haemoglobins form *in vivo*. In this family haemoglobin G (Hb–G) with abnormal α-chains, and haemoglobin C (Hb–C) with abnormal β-chains, segregate independently. Two of its members possess four major haemoglobins, which are Hb–A, Hb–G, Hb–C, and the doubly abnormal haemoglobin G/C ($\alpha_2^G\beta_2^C$), the last resulting from the combination of the abnormal subunits of Hb–G and Hb–C.

Methods

Haematological examination was by standard methods.

Foetal haemoglobin was estimated by the method of Singer *et al.* (1951).

Electrophoresis on cellulose acetate was as described by Kohn (1957), using diethyl barbiturate buffer of *p*H 8.6 and ionic strength 0.05.

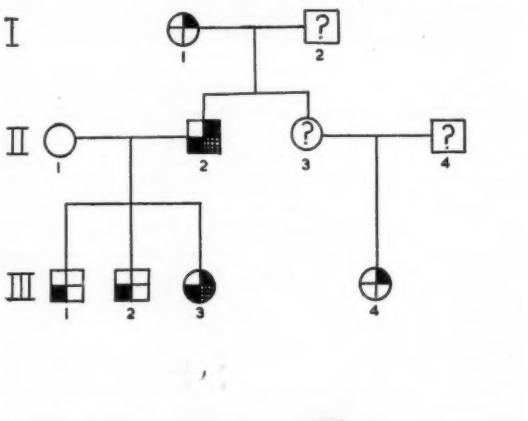
Electrophoresis on starch block followed the method of Kunkel (1954), and *in starch gel* the method of Smithies (1955) using either the discontinuous buffer system (Poulik, 1957) or a phosphate buffer system (Huehns *et al.*, 1960). The haemoglobin zones in starch gel were detected with *o*-dianisidine (Owen *et al.*, 1958). After separation of the haemoglobin zones on starch block the appropriate zone was cut out and the haemoglobin eluted from the starch with 0.02M sodium chloride. The haemoglobin was reconverted to the carbonmonoxy form, its concentration determined by measuring the optical density at 570 mμ, and the solution subsequently concentrated in $\frac{1}{4}$-in. (6.4-mm.) dialysis tubing *in vacuo* in the cold, being simultaneously dialysed against 0.02M saline.

Chromatography on the ion-exchange resin IRC 50 followed the procedure of Huisman and Prins (1955).

Hybridization of haemoglobins was carried out according to the principle described by Itano and Singer (1958), but on the microscale devised by Gammack *et al.* (1960).

Family Studies

The propositus (III-3 on accompanying family tree) was a female child, aged 1 year, of immigrant Barbadoan negro parents, who presented with an upper respiratory



The family tree.

tract infection. No abnormal physical signs were found except those of the above infection. Liver and spleen could not be felt. She was found to have an iron-deficiency anaemia; haemoglobin 10.4 g. per 100 ml., and serum iron 24 μg. per 100 ml. (see Table). The blood film showed red cells with moderate anisocytosis, hypochromia, and some target cells. Electrophoresis of a haemolysate on cellulose acetate showed four equally spaced haemoglobin bands. Three of these were identified as Hb–A, Hb–G, and Hb–C; the fourth was distinctly slower than Hb–C. The child was treated with iron by mouth for a period of two months, during which no significant rise in the total haemoglobin concentration

occurred; however, some fully haemoglobinized cells were visible in the blood film at the end of this period.

The unique appearance of four haemoglobins in one person led to the investigation of the family (see figure). The father (II-2) was also found to have the same four haemoglobins (Special Plate, Fig. 1*d*). He was healthy and there was no history of anaemia. The spleen could not be felt. His haemoglobin was 17.8 g. per 100 ml. and his blood film appeared normal (see Table). The mother carried only Hb–A (Special Plate, Fig. 1*c*) and was haematologically normal (see Table). The red cells from these subjects did not sickle. Other members of the family had remained in Barbados, but with the co-operation of Drs. J. MacIver and L. E. Went and their colleagues blood was obtained from two brothers (III-1 and III-2) of the propositus, her paternal grandmother (I-1), and a female cousin (III-4). Drs. MacIver and Went have shown that III-1 and III-2 both carry the Hb–C trait, while subsequent investigation in Britain revealed that I-1 and III-4 both carry the Hb–G trait (Special Plate, Fig. 1*a* and *b*). In all cases the percentage of foetal haemoglobin was within normal limits.

Experimental Studies

Identification of Haemoglobins

Electrophoresis of the haemolysate of the propositus of her father on both cellulose acetate and in starch gel (Special Plate, Fig. 1*d* and *e*) showed four haemoglobin bands, one migrating in the position of Hb–A, one slightly faster than Hb–S, one in the position of Hb–C, and one slower than Hb–C. The minor haemoglobin band migrating in front of Hb–A in the haemolysates of II-2 and III-3 as well as of II-1 is Hb–A_2, which is often found in association with Hb–A and is presumed to be derived from it (Kunkel and Bearn, 1957). The same four major bands appeared on starch block, and the identity of the faster three zones with Hb–A, Hb–G, and Hb–C was confirmed by elution of these zones and subsequent chromatography on IRC 50 resin (Special Plate, Fig. 2). The fourth zone was similar on chromatography to Hb–C. In addition, the haemoglobin in the third and fourth zones was rapidly converted from carbonmonoxyhaemoglobin to methaemoglobin, a characteristic property of Hb–C. In order to distinguish the haemoglobin G in this paper from those previously reported (Edington *et al.*, 1955; Schwartz *et al.*, 1957; Gammack *et al.*, 1960) it will be called haemoglobin $G_{Bristol}$(Hb–G_{Br}).

The proportions of the four haemoglobins in II-2 determined after elution of the separated zones from starch block were 43%, 23%, 23%, and 11% of the total haemoglobin for Hb–A, Hb–G_{Br}, Hb–C, and the slowest haemoglobin, respectively. The composition of the haemolysate of the propositus (III–3) appeared from the starch-gel analyses (Special Plate, Fig. 1*d* and *e*) to be similar. The Hb–G_{Br}-trait III-4 had 55% Hb–A and 45% Hb–G_{Br}.

Hybridization Experiments

Dissociation and recombination of a solution containing the two haemoglobins G_{Br} and C from II-2 produced two new haemoglobin species migrating in the positions of the fastest and slowest haemoglobin zones of II-2 (Special Plate, Fig. 3*c*, *d*, and *e*). Similarly, after hybridization of the haemoglobin in the fastest (Hb–A) and slowest zones, two additional haemoglobin bands appeared in positions corresponding to the intermediate haemoglobins G_{Br} and C (Special Plate, Fig. 3*a*, *b*, and *c*). In this latter experiment the original solution of the slowest haemoglobin was contaminated with the next fastest haemoglobin, Hb–C, but the increase in Hb–C as well as the new appearance of Hb–G_{Br} can be seen clearly in the figure. In contrast to these results neither a new haemoglobin species nor an increase in any existing species was found when the slowest haemoglobin fraction was hybridized with either of the two intermediate fractions, Hb–G_{Br} or Hb–C (Special Plate, Fig. 4*d*, *e*, and *a*, *b*). The Hb–C and Hb–G_{Br}/C zones in the artificial mixtures of these experiments migrated rather more slowly than the corresponding zones in the haemolysate. A displacement effect of this sort is often observed, however, when the concentrations of the individual haemoglobins in the various solutions being analysed are not identical (Butler *et al.*, 1960).

Discussion

Composition of the Slowest Migrating Haemoglobin

It is clear from the family study that the Hb–G_{Br} and Hb–C in this family segregate independently. The appearance of new species in the experimental hybridization of Hb–G_{Br} with Hb–C (Special Plate, Fig. 3*d* and *e*) suggests that one of these haemoglobins has abnormal α-chains and the other abnormal β-chains. Since Hb–C has been shown to have abnormal β-chains (Hunt and Ingram, 1959), then the Hb–G_{Br} in this family must be abnormal in the α-chains. This allocation of chain abnormality has been confirmed by separate experiments with the Hb–G_{Br} and Hb–C. Thus, when Hb–G_{Br} was hybridized with Hb–S, a variant known to have abnormal β-chains (Hunt and Ingram, 1959), a new haemoglobin species appeared near the position of Hb–C and a zone of increased density appeared in the position of Hb–A (Special Plate, Fig. 5). The latter zone is partially obscured by the foetal haemoglobin present in the specimen from a case of sickle-cell anaemia used in this experiment and by the Hb–A contaminating the eluted Hb–G_{Br}, both of which produce the diffuse zone in front of the GS band in the untreated mixture. This experiment, therefore, shows that Hb–G_{Br} has abnormal α-chains. It would appear that this haemoglobin is possibly another example of the Hb–G with abnormal α-chains (haemoglobin G_{Ibadan}) described by Gammack *et al.* (1960). Hybridization of Hb–C with Hb–H, which consists of four β^A-chains (Jones *et al.*, 1959) produced

Table Showing the Haematological Findings in the Propositus and Her Parents

	Age (Years)	Hb (g. per 100 ml.)	Packed Cell Volume (%)	Red Cells (Millions per c.mm.)	M.C.D. (μ)	M.C.V. ($c\mu$)	M.C.H.C. (g. per 100 ml.)	M.C.A.T. (μ)	Reticulocytes (%)	Alk. Res. Hb (%)	Haemoglobin Types	Anisocytosis	Hypochromia	Target Cells
Propositus	1	10·4	31	5·1	7·6	61	33	1·34	2·1	2·2	A+G_{Br}+C +G_{Br}/C	+	+	++
Father ..	36	17·8	49	6·4	7·0	78	36	2·0	...	1·0	A+G_{Br}+C +G_{Br}/C	0	0	0
Mother ..	24	14·1	43	4·6	7·0	94	33	2·4	...	0·8	A	tr.	0	0

Hb–A (Special Plate, Fig. 6), from which it can be concluded that Hb–C has normal α-chains, and therefore by inference abnormal β-chains.

$$\underset{\text{Hb–C}}{2\alpha_2{}^{A}\beta_2{}^{C}} + \underset{\text{Hb–H}}{\beta_2{}^{A}\beta_2{}^{A}} \longrightarrow \underset{\text{Hb–C}}{\alpha_2{}^{A}\beta_2{}^{C}} + \underset{\text{Hb–A}}{\alpha_2{}^{A}\beta_2{}^{A}} + (\beta_2{}^{C} + \beta_2{}^{A})$$

The fate of the subunits enclosed in brackets in this equation has not been determined.

It is probable, therefore, that the composition of the two new haemoglobins formed in the hybridization of Hb–G_{Br} with Hb–C are $\alpha_2{}^{A}\beta_2{}^{A}$ (Hb–A) and $\alpha_2{}^{G_{Br}}\beta_2{}^{C}$, a doubly abnormal haemoglobin, now called Hb–G_{Br}/C, which carries the sum of the charges of the parent species HB–G_{Br} and Hb–C.

$$\underset{\text{Hb–}G_{Br}}{2\alpha_2{}^{G_{Br}}\beta_2{}^{A}} + \underset{\text{Hb–C}}{2\alpha_2{}^{A}\beta_2{}^{C}} \longrightarrow \underset{\text{Hb–A}}{\alpha_2{}^{A}\beta_2{}^{A}} + \underset{\text{Hb–}G_{Br}}{\alpha_2{}^{G_{Br}}\beta_2{}^{A}} + \underset{\text{Hb–C}}{\alpha_2{}^{A}\beta_2{}^{C}} + \underset{\text{Hb–}G_{Br}\text{/C}}{\alpha_2{}^{G_{Br}}\beta_2{}^{C}}$$

Difference in net charge from Hb–A :—

$$\underset{+2}{} \quad \underset{+4}{} \quad \underset{0}{} \quad \underset{+2}{} \quad \underset{+4}{} \quad \underset{+6}{}$$

It can be seen in Fig. 3 of the Special Plate that these two new species, Hb–A and Hb–G_{Br}/C, migrate at the same rate as the fastest and slowest of the four haemoglobins occurring *in vivo*. This suggests that the slowest haemoglobin of II-2 is identical with the doubly abnormal haemoglobin G_{Br}/C produced in the above *in-vitro* hybridization. If this is so, then dissociation and recombination of the slowest haemoglobin with Hb–A would be expected, as shown in the following equation, to re-form the two singly abnormal haemoglobins, G_{Br} and C, which are found in the haemolysates of the propositus and her father.

$$\underset{\text{Hb–}G_{Br}\text{/C}}{2\alpha_2{}^{G_{Br}}\beta_2{}^{C}} + \underset{\text{Hb–A}}{2\alpha_2{}^{A}\beta_2{}^{A}} \longrightarrow \underset{\text{Hb–A}}{\alpha_2{}^{A}\beta_2{}^{A}} + \underset{\text{Hb–}G_{Br}}{\alpha_2{}^{G_{Br}}\beta_2{}^{A}} + \underset{\text{Hb–C}}{\alpha_2{}^{A}\beta_2{}^{C}} + \underset{\text{Hb–}G_{Br}\text{/C}}{\alpha_2{}^{G_{Br}}\beta_2{}^{C}}$$

The starch-gel analyses of this particular hybridization experiment (Special Plate, Fig. 3*a*, *b*, and *c*) have confirmed that Hb–G_{Br} and Hb–C are indeed re-formed. On the other hand, no change in composition would be expected if the slowest haemoglobin were hybridized with either of the singly abnormal haemoglobins G_{Br} and C, because the latter two have either the same abnormal α_2 or abnormal β_2 subunit as the doubly abnormal haemoglobin G_{Br}/C. Again, this expectation has been confirmed by the experiments illustrated in Special Plate, Fig. 4. Although in both experiments the hybridized mixtures are somewhat less concentrated than the untreated mixtures, because of precipitation of some haemoglobin in the dialysis of the acidified solutions, no real differences can be seen in the composition of the corresponding hybridized and untreated mixtures. It is thus clear that the propositus and her father possess a doubly abnormal haemoglobin, G_{Br}/C, composed of the abnormal $\alpha_2{}^{G}$ and $\beta_2{}^{C}$ subunits of Hb–G_{Br} and Hb–C respectively. In addition, they have two singly abnormal haemoglobins, G_{Br} and C, as well as haemoglobin A.

The in vivo Synthesis of the Four Haemoglobins

Since the propositus received genes for both Hb–G_{Br} and Hb–C from her father, they must presumably occur at different loci. This same situation has been found in at least two other families. In the one described by Schwartz *et al.* (1957) the child, by a normal person, of the propositus, who was heterozygous for Hb–S and another type of Hb–G (as well as for thalassaemia), had neither Hb–S nor Hb–G. In the second family (Smith and Torbert, 1958) the child of a normal father and a mother with Hb–S and Hb–Ho.2 had Hb–S, Hb–Ho.2, and a third fraction migrating in the position of Hb–A —the fraction which Itano *et al.* suggest may contain both Hb–A and the doubly abnormal haemoglobin S/Ho.2.

If it is accepted that the synthesis of the α- and β-chains of a haemoglobin molecule are controlled by pairs of genes at different loci, then the genotype for a person with normal adult haemoglobin may be written α^{A}/α^{A}, β^{A}/β^{A} (Ingram and Stretton, 1959) Since the propositus and her father possess two abnormal haemoglobins, Hb–G_{Br} with abnormal α-chains and Hb–C with abnormal β-chains, determined by genes at different loci, their genotype is $\alpha^{A}/\alpha^{G_{Br}}$, β^{A}/β^{C}. They would therefore be capable of synthesizing four types of chains, the normal α^{A}- and β^{A}-chains as well as the abnormal $\alpha^{G_{Br}}$- and β^{C}-chains. Now, Itano *et al.* (1959) have pointed out that the absence of hybrid haemoglobins of the type $\alpha_2{}^{A}\beta^{A}\beta^{C}$ (where, in this example, unlike β-chains are paired) both *in vivo* and in the *in-vitro* hybridization experiments means either that a single polypeptide chain once synthesized rapidly combines with another chain of the same type to form α_2 or β_2 subunits, or alternatively that the chains are synthesized in stable identical pairs. In any event, individuals with this abnormal genotype will synthesize the four different types of subunit $\alpha_2{}^{A}$, $\beta_2{}^{A}$, $\alpha_2{}^{G_{Br}}$, and $\beta_2{}^{C}$, and they will then possess all the subunits necessary for the subsequent synthesis of the four complete haemoglobins.

The final stage in the synthesis of the haemoglobin molecule on this hypothesis is the association of α_2 and β_2 subunits. If the α_2 and β_2 subunits have the same affinity for one another irrespective of type, then the amount of each of the four haemoglobins formed will be determined by the numbers of subunits present at any given time—that is, by their relative rates of synthesis. Itano (1957) has suggested that when an abnormal haemoglobin occurs together with Hb–A the proportion of this haemoglobin that appears in the haemolysate is determined by its rate of synthesis relative to that of Hb–A. Since the heterozygotes for Hb–G_{Br} and Hb–C both show less than 50% of the abnormal haemoglobin (the actual figure for the Hb–G_{Br} is 45% and that for Hb–C traits usually falls between 30% and 45%), it can be inferred that the rate of synthesis of each of these variants is less than that of Hb–A. This carries the further implication that the rate of synthesis of the abnormal subunit is less than that of its normal counterpart and is the rate-limiting step in the formation of the abnormal haemoglobin. Therefore, in the propositus and her father the rates at which the normal $\alpha_2{}^{A}$ and $\beta_2{}^{A}$ subunits are being synthesized are greater than for either $\alpha_2{}^{G_{Br}}$ or $\beta_2{}^{C}$. It follows that at the association step more $\alpha_2{}^{A}\beta_2{}^{A}$ (Hb–A) will be formed than either $\alpha_2{}^{G_{Br}}\beta_2{}^{A}$ (Hb–G_{Br}) or $\alpha_2{}^{A}\beta_2{}^{C}$ (Hb–C). However, it is also true that, because of the relative profusion of $\alpha_2{}^{A}$ and $\beta_2{}^{A}$ subunits, more of the abnormal $\alpha_2{}^{G_{Br}}$ and $\beta_2{}^{C}$ subunits will combine with them to form Hb–G_{Br} and Hb–C than for each other to form Hb–G_{Br}/C, and as a consequence the proportion of the latter will be even less than that of Hb–G_{Br} or Hb–C. It will be noted that the actual proportions found in the father—43% Hb–A, 23% Hb–G_{Br}, 23% Hb–C, and 11% Hb–G_{Br}/C—fall in the order anticipated from the above reasoning.

In contrast, it is unlikely that the four haemoglobins would be found in these proportions if each whole haemoglobin molecule was synthesized independently. Its rate of synthesis would in this event be determined by the formation of the subunit with the lower rate of synthesis. In other words, the amount of Hb–G_{Br}/C formed would be determined by the rate of synthesis of the $\alpha_2{}^{G_{Br}}$ or $\beta_2{}^{C}$ subunit, whichever was the slower, and

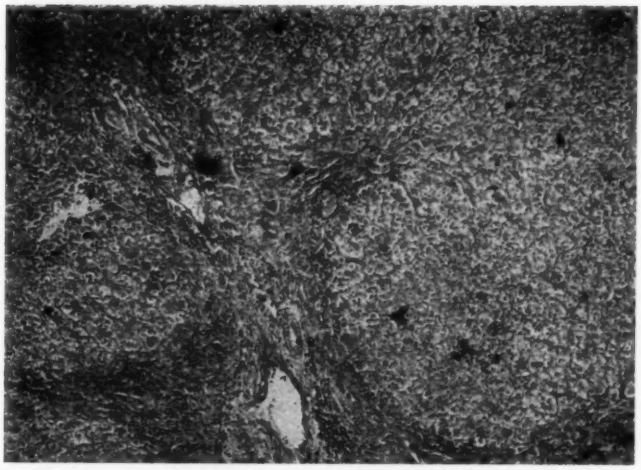


Fig. 1.—Liver from first biopsy, showing wide interlobular bands composed of proliferating small bile-ducts, reticulin and collagen fibres, and clumps of lymphocytes and macrophages. Much bile stasis in the lobules. (H. and E. ×60.)

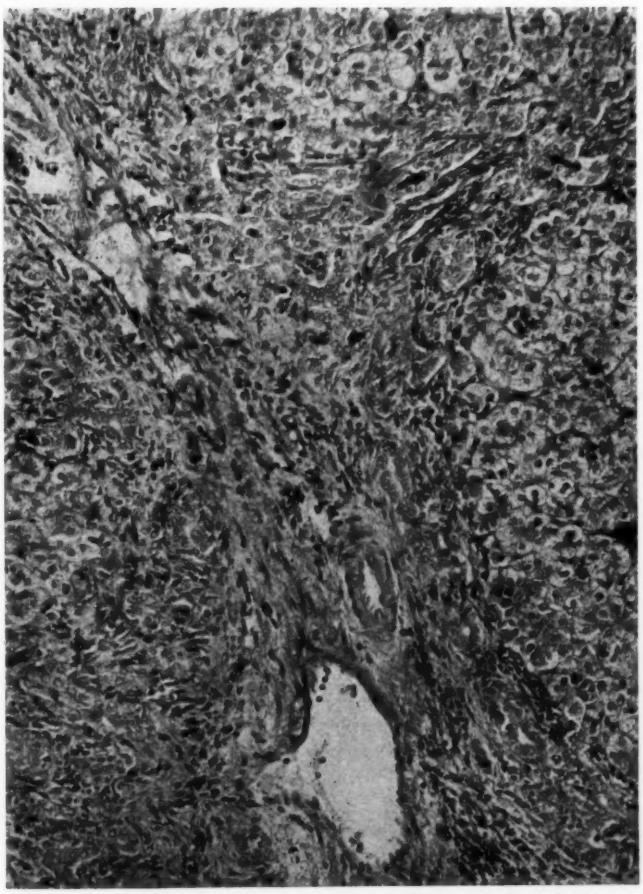


Fig. 2.—Detail of Fig. 1 showing bile-duct hyperplasia, reticulin and collagen bands, and much bile stasis. (H. and E. ×120.)

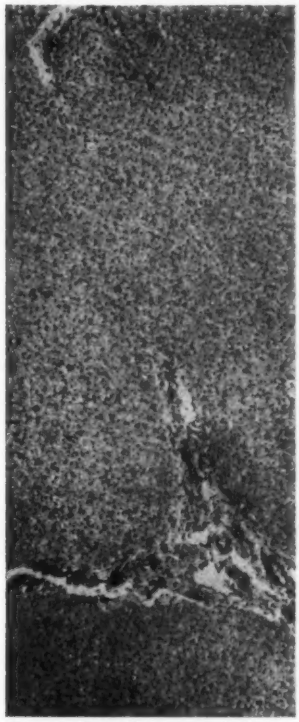


Fig. 3.—Liver from second biopsy, showing normal structure. (H. and E. ×60.)

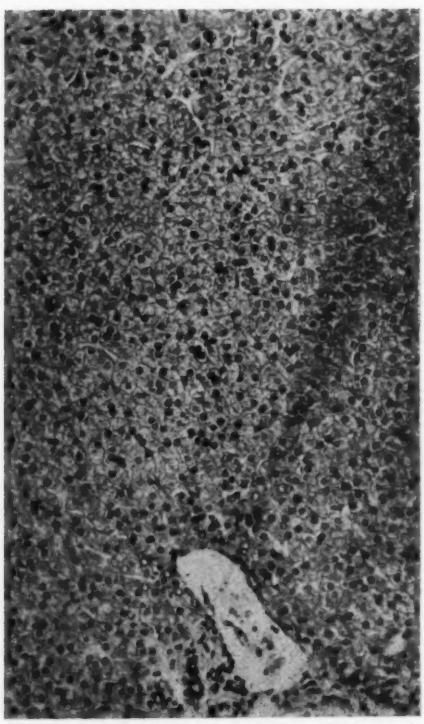


Fig. 4.—Detail of Fig. 3 showing normal portal tract and liver cells. (H. and E. ×120.)

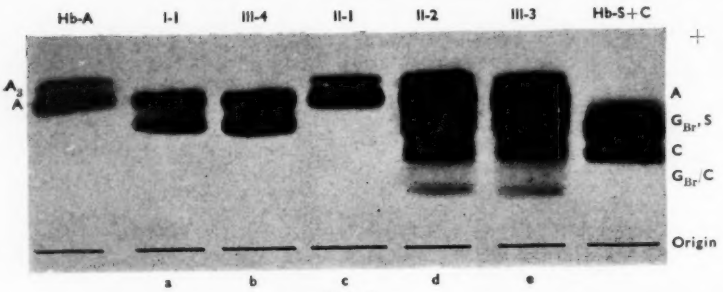


FIG. 1

FIG. 1.—Electrophoresis in starch gel of the haemolysates of some members of the family. Discontinuous tris citrate–borate system.

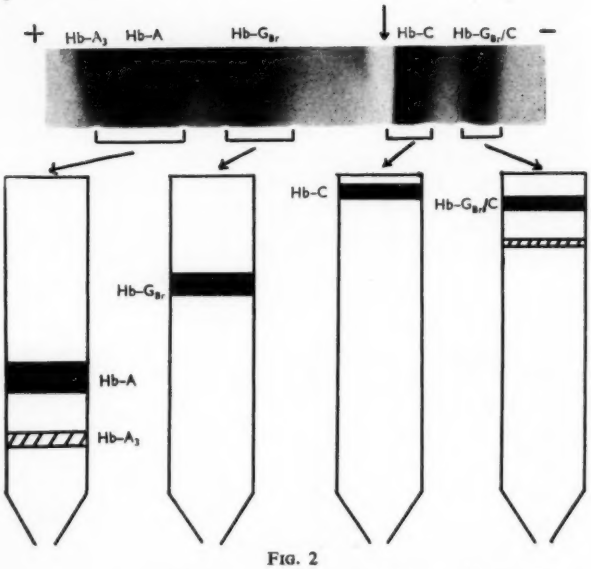


FIG. 2

FIG. 2.—Starch-block electrophoresis of haemolysate of father of propositus (II-2) with subsequent chromatography on IRC 50.

FIG. 3.—Hybridization of isolated haemoglobins from II-2. Electrophoretic analysis in starch gel in the discontinuous tris citrate–borate system. (*a*) Untreated mixture of isolated Hb-A and Hb-G_{Br}/C. (*b*) Mixture of Hb-A and Hb-G_{Br}/C, dissociated and recombined. (*c*) Natural haemolysate from II-2. (*d*) Mixture of Hb-G_{Br} and Hb-C dissociated and recombined. (*e*) Untreated mixture of isolated Hb-G_{Br} and Hb-C.

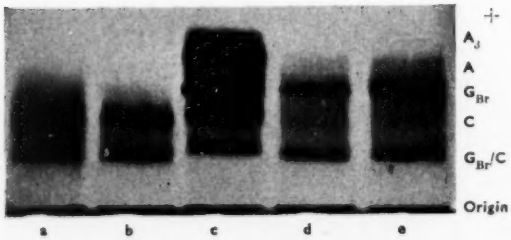


FIG. 4.—Hybridization of isolated haemoglobins from II-2. Electrophoretic analysis in starch gel in the discontinuous tris citrate–borate system. (*a*) Untreated mixture of isolated Hb-C and Hb-G_{Br}/C. (*b*) Mixture of Hb-C and Hb-G_{Br}/C dissociated and recombined. (*c*) Natural haemolysate from II-2. (*d*) Mixture of Hb-G_{Br} and Hb-G_{Br}/C dissociated and recombined. (*e*) Untreated mixture of isolated Hb-G_{Br} and Hb-G_{Br}/C.

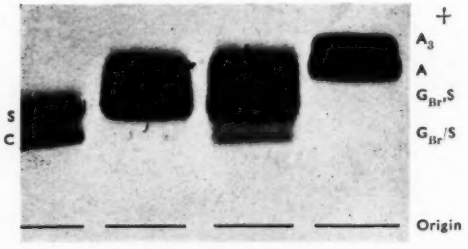


FIG. 5.—Hybridization of isolated Hb-G_{Br} with Hb-S. Electrophoretic analysis in starch gel in the discontinuous tris citrate–borate system. (*a*) Hb-S + Hb-C marker. (*b*) Untreated mixture of Hb-G_{Br} and Hb-S. (*c*) Mixture of Hb-G_{Br} and Hb-S dissociated and recombined. (*d*) Hb-A marker.

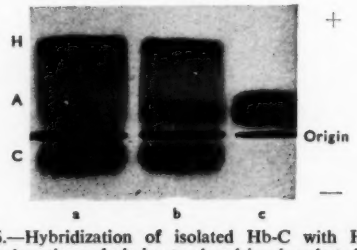


FIG. 6.—Hybridization of isolated Hb-C with Hb-H. Electrophoretic analysis in starch gel in phosphate buffer *p*H 7.4. (*a*) Untreated mixture of Hb-C and Hb-H. (*b*) Mixture of Hb-C and Hb-H dissociated and recombined. (*c*) Hb-A marker.

would finally be equal to the amount of either Hb–G_{Br} or Hb–C. However, in both individuals who possess the four haemoglobins the proportion of Hb–G_{Br}/C is significantly less than that of Hb–G_{Br} or Hb–C.

The further possibility that four haemoglobins could be formed by the synthesis of the two abnormal haemoglobins followed by an intracellular exchange of the subunits has also been raised (Itano *et al.*, 1959). However, on this hypothesis the proportion of Hb–G_{Br}/C would be the same as that of Hb–A, and this again is not so.

The results obtained from the study of this family therefore support the idea that haemoglobin synthesis is controlled by at least two pairs of genes. Furthermore, they suggest that each individual gene finds expression in its own "template," which in turn determines (in effect) the synthesis of a particular type of subunit. These independently synthesized subunits subsequently associate to produce the haemoglobins found in the red cell. If there is a mutation of one gene, as, for example, in the Hb–C trait, the genotype is α^A/α^A, β^A/β^C, resulting in the formation of $\alpha_2{}^A$, $\beta_2{}^A$, and $\beta_2{}^C$ subunits and the subsequent production of Hb–A and Hb–C. When two mutations are present three different situations can arise. First, if the same mutation occurs twice—for example, the genotype is α^A/α^A, β^C/β^C—only the subunits $\alpha_2{}^A$ and $\beta_2{}^C$ of Hb–C are made. On the other hand, when the two mutations are different but occur at the same locus—for example, the genotype is α^A/α^A, β^S/β^C—the subunits $\alpha_2{}^A$, $\beta_2{}^S$, and $\beta_2{}^C$ are made, and this leads to the formation of Hb–S and Hb–C. Finally, if two different mutations occur, one on each locus, as in the propositus of this family—for example, the genotype is $\alpha^A/\alpha^{G_{Br}}$, β^A/β^C—four different types of subunits, $\alpha_2{}^A$, $\alpha_2{}^{G_{Br}}$, $\beta_2{}^A$, and $\beta_2{}^C$, are formed and the four haemoglobins species A, G_{Br}, C, and G_{Br}/C result.

Clinical Features

The propositus had a haematological picture typical of a haemoglobinopathy in that she showed a mild anaemia with target cells in the peripheral-blood smear. Further investigation also revealed concomitant iron deficiency. Her father had the same haemoglobin abnormality, but had no anaemia, and his blood film appeared normal. It seems, therefore, that in this case the anaemia was due to iron deficiency only, and the appearance of target cells was due to haemoglobinopathy and iron deficiency acting together. Her response to oral administration of iron was slow, but one would expect her to reach an almost normal blood picture eventually.

Summary

A family in which two persons carry four haemoglobins—namely, haemoglobins A, G_{Br}, C, and the previously undescribed haemoglobin G_{Br}/C—has been investigated in detail. It has been shown that Hb–G_{Br} and Hb–C segregate independently, and that in the former the α-chains are abnormal and in the latter the β-chains are abnormal. Haemoglobin G_{Br}/C is doubly abnormal, being composed of the abnormal $\alpha_2{}^{G_{Br}}$ subunit of Hb–G_{Br} and the abnormal $\beta_2{}^C$ subunit of Hb–C. The relative proportions of the four haemoglobins found in the propositus suggest that association of the α_2 and β_2 subunits is the final step in haemoglobin synthesis.

One of us (D. B. G.) wishes to acknowledge financial assistance from the Colonial Medical Research Committee. We are grateful to Dr. J. Apley for allowing us access to his clinical notes, and to Dr. E. M. Crook for helpful discussions.

ADDENDUM.—Since this paper went to press, Atwater, Schwartz, and Tocantins have independently described a family in which two members possess the four haemoglobins Hb–A, Hb–G_{Porter}, Hb–C, and a fourth of undetermined composition. These authors point out that, if it is assumed that Hb–G_{Porter} has abnormal α-chains, then the fourth haemoglobin could have the composition $\alpha_2{}^G\beta_2{}^C$.

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The Grenfell Mission provides a medical and social service for the fishermen, Indians, and Eskimos who live along the 2,000-mile coastline of northern Newfoundland and Labrador. The Mission is now using aircraft to bring medical treatment within the reach of everyone for the first time in the history of the country. In the days of travel by boat and dog team many were too isolated to receive even an occasional visit from a doctor or nurse, let alone regular treatment, and patients often reached the mission hospitals too late after days spent in open boats or travelling by dog team. Even to-day, maintaining a medical and social service in a subarctic country is not an easy task, and travel by land, sea, or air is still fraught with dangers and difficulties. Christmas cards are being sold to enable the work of the Mission to be expanded, and a catalogue of these—including one of Grenfell with his huskies—is now obtainable from the Secretary, Grenfell Association of Great Britain and Ireland, Hope House, Great Peter Street, London S.W.1.

HAEMOGLOBIN O IN AN ARAB FAMILY

SICKLE-CELL HAEMOGLOBIN O TRAIT

BY

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An 8-year-old Arab boy from the village of Gaser A'zarka, in Israel, was admitted to the paediatric service of Chedera General Hospital, and found to be suffering from a left-lower-lobe pneumonia. The patient was said to have had attacks of abdominal pain about once every year, mainly in the right hypochondrium. These attacks were accompanied by jaundice and dark urine. Several days before admission such an attack had occurred.

On physical examination the boy was pale and jaundiced. In addition to the finding of pneumonia, an enlarged spleen was palpable 4 cm. below the costal margin.

Blood Examination

The peripheral blood smear showed anisocytosis, poikilocytosis, target cells, and occasional sickle-cells. The haematological findings are summarized in the Table. The haemoglobin was examined by the method of Singer, Chernoff, and Singer (1951), and 10% was found to be alkali-resistant by this method.

On paper electrophoresis at *p*H 9, using TRIS buffer, two fractions were seen, one in the position of haemoglobin A and one moving more slowly. The second fraction amounted to about 70% of the total, and the picture was very much like that seen in sickle-cell thalassaemia. It was, however, noteworthy that the "haemoglobin S fraction" seemed to be moving slightly more slowly than haemoglobin S controls. It was, in fact, only a little in advance of haemoglobin C (Fig. 1).

On paper electrophoresis at *p*H 8.6, using barbiturate buffer, three abnormal fractions were noted: one in the position of haemoglobin A+F, one in the position of haemoglobin S, and a third which did not separate well from the haemoglobin S fraction and which moved more slowly than S and faster than haemoglobin C (Fig. 2). Comparison with haemoglobin S+E samples showed that the slowest fraction was faster than E and therefore in the position of haemoglobin O (Lie-Injo Luan Eng and Sadono, 1958). Direct comparison with

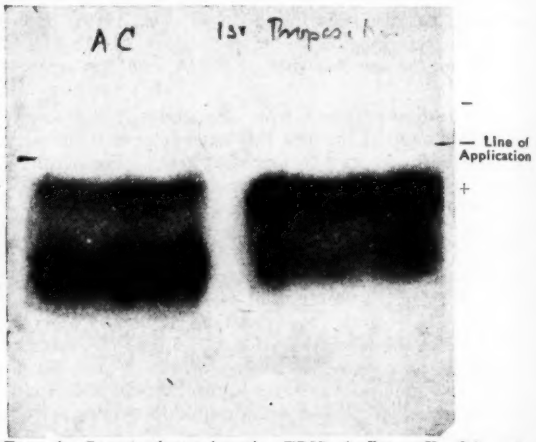

FIG. 1.—Paper electrophoresis TRIS buffer, *p*H 8.9, of propositus's haemoglobin and A+C control. The propositus's haemoglobin divides into two fractions, one corresponding to A+F and one moving more slowly.

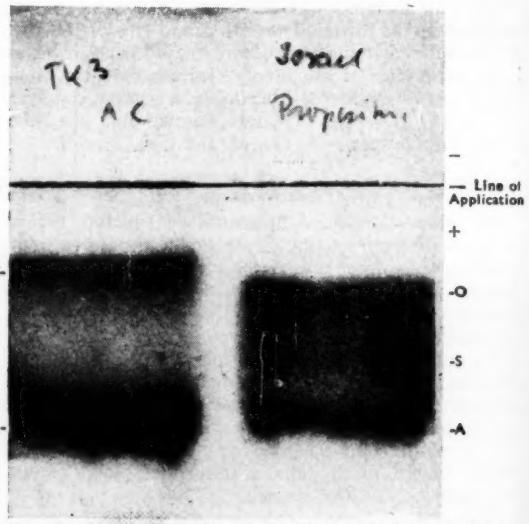

FIG. 2.—Paper electrophoresis barbiturate buffer, *p*H 8.6, of propositus's haemoglobin and A+C control. The propositus's haemoglobin divides into three fractions, one corresponding to A+F, one in the position of S, and one moving between C and S in the position of haemoglobin O.

Findings in a Family in which Haemoglobins A, S, and O are Found as Adult Variants

	Age in Years	Sickle-cell Test	Adult Haemoglobins	Alkali-resistant Haemoglobin (%)	Red Cells (Million/c.mm.)	Haemoglobin (g./100 ml.)	Cell Volume (%)	M.C.H.C. (%)	M.C.V. (cu.μ)	M.C.H. (μμg.)	Reticulocytes (%)
Father	28	0	AO	1·9	4·6	14·9	46	31	100	32	1·2
Mother	?	+	AS	1·7	3·5	10·5	35	33	100	30	0·8
Mother's mother	67	0	A	3·7	4·1	11·4	40	35	98	28	0·9
Propositus ..	8	+	SOA	10	2·5	7·0	25	36	100	28	32
Sister 1	4	+	SOA	28	2·8	8·6	31	36	110	31	8
„ 2	3	0	AO	—	—	—	—	—	—	—	—
„ 3	2/12	0	AS	59	3·4	10·6	34	32	100	31	7

a haemoglobin A+O sample, which had kindly been supplied by Dr. Lie-Injo Luan Eng, also confirmed that the third haemoglobin had the mobility of haemoglobin O. Haemoglobin Alexandra has the same mobility under these conditions, but it can be differentiated from O by electrophoresis on agar at *p*H 6, when Alexandra moves with F. It could also be demonstrated that on the addition of haemoglobin S to a haemoglobin A+O mixture a similar picture could be obtained on paper electrophoresis using barbiturate buffer, and, furthermore, that haemoglobins S and O formed a single band on paper electrophoresis using TRIS buffer. On ion-exchange chromatography, using IRC 50 at *p*H 6, haemoglobins F, A, S, and O could be demonstrated. Haemoglobins S and O amounted to about one-third each. There was also a small amount of haemoglobin A_2 moving between haemoglobins A and S. These findings suggest that the patient suffered from a modified sickle-cell anaemia of a type hitherto not described—a combination of the traits for haemoglobins S and O.

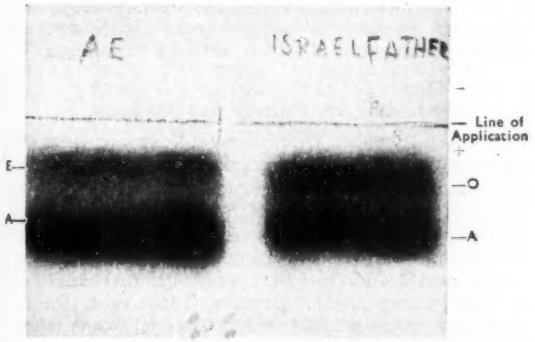

FIG. 3.—Paper electrophoresis TRIS buffer, *p*H 8.9, of the father's haemoglobin and A+E control. The father's haemoglobin divides into two fractions, one in the position of A and one moving faster than E. Other electrophoretic comparisons had shown that the non-A haemoglobin of the father moved under these conditions more slowly than haemoglobin S.

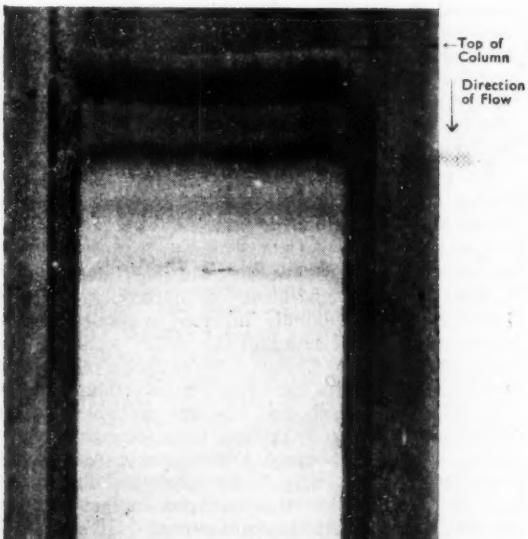

FIG. 4.—Chromatography IRC 50, *p*H 6, of sister's haemoglobin. Starting from below, haemoglobins F, A, S, and O can be seen.

There were no other striking findings in this patient's blood. Total serum protein was 8.3 g./100 ml. (albumin 5.2 g., globulin 3.1 g.). Serum thymol turbidity and cephalin cholesterol turbidity were 4 units and 0 respectively.

Patient's Family.—The parents, the maternal grandmother, and three siblings were investigated. Two siblings had died in infancy. The haematological findings, so far as could be obtained, are included in the Table. Examination of the haemoglobin showed that the father was a haemoglobin O trait carrier (Fig. 3), and the mother a sickle-cell trait carrier. One sibling was a sickle-cell trait carrier, one a haemoglobin O trait carrier, and one possessed haemoglobins F, A, A_2, S, and O (Fig. 4). One notable fact was that the patient's grandmother had a more than normal amount of foetal haemoglobin (3.7%), otherwise no abnormalities were found in her. The older sister, who also suffered from sickle-cell haemoglobin O "disease," had a higher percentage of haemoglobin F (28%) and a small amount of haemoglobin A (8%). The remainder consisted of about equal parts of haemoglobin S and O (Fig. 5).

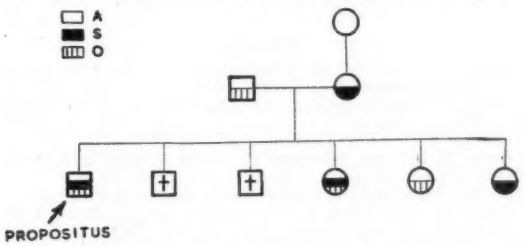

FIG. 5.—Family tree. Haemoglobins A, S, and O.

Discussion

Haemoglobin O was discovered by Lie-Injo Luan Eng and Sadono (1958) in Indonesia, and has hitherto not been found in any other part of the world. The exact ethnic origin of the Arab family described in this report could not be established, but it is noteworthy that another East Asian haemoglobin, haemoglobin E, has been observed sporadically in the Eti-Turks (Aksoy, Ikin, Mourant, and Lehmann, 1958). Until now it had not been possible to study the mode of inheritance of haemoglobin O, and the present investigation demonstrates that it is inherited in a Mendelian fashion, and that when it is inherited with haemoglobin S haemoglobin A is formed as well.

The presence of haemoglobin A together with S and one other abnormal haemoglobin has been noted before with Hopkins II (Smith and Torbert, 1958) and P (Dherte, Lehmann, and Vandepitte, 1959). Ingram (1959) suggested that there was one gene determining the formation of the α-chain and one determining the formation of the β-chain. Thus if an individual inherited an abnormal haemoglobin in which the α-chain was different from the normal he would still possess a normal β-chain, and if he also inherited another abnormal haemoglobin in which the β-chain was abnormal he would still possess a normal α-chain. This would enable him to form three haemoglobins—the abnormal α-chain haemoglobin, the abnormal β-chain haemoglobin, and a haemoglobin formed by the normal α- and β-chains: haemoglobin A.

Itano and Robinson (1959) dissociated a mixture of haemoglobin Hopkins II, which carries its abnormality

in the α-chain, and of haemoglobin S, which carries its abnormality in the β-chain into α- and β-chains. On recombination they obtained haemoglobin A as well as a hybrid composed of abnormal α- and β-chains. One might therefore expect that when haemoglobin S and another abnormal haemoglobin are found together with haemoglobin A, S being a β-chain mutant, the other abnormal haemoglobin would be an α-chain mutant. We have reason to believe, however, that haemoglobin O is not an α-chain mutant, and indeed the same applies to haemoglobin P. A full account of this will be given by two of us (B.R. and H.L.) in collaboration with Drs. E. M. Shooter and E. R. Huehns, of University College, London, and a tentative explanation for this apparent paradox will then be put forward.

Summary

A new sickling condition—sickle-cell haemoglobin O trait—has been demonstrated in two children of an Arab family. This is the first occasion on which haemoglobin O has been seen outside Indonesia and that its mode of inheritance could be examined.

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A CASE OF SUBACUTE RICKETTSIAL ENDOCARDITIS; WITH A SURVEY OF CARDIAC PATIENTS FOR THIS INFECTION

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A few reports during the last 10 years suggest that Q fever in man sometimes pursues a chronic course with infection of the heart valves. Marmion *et al.* (1953) reviewed three possible cases of the condition—two Californian patients and one English.

More recently it was possible to observe the course of the disease during a two-year period in a patient of Dr. F. H. Scadding's at the Middlesex Hospital, London. A brief description of the findings was given at the Sixth International Congress of Tropical Medicine and Malaria (see Marmion, 1958), and a detailed account has been published together with a review of the literature on persistent Q fever infections (Robson and Shimmin, 1959; Andrews and Marmion, 1959). The patient was a man aged 47, who had pneumonia clinically resembling Q fever, recovered, and was apparently healthy for six months, then became chronically ill with a swinging fever. Aortic valve incompetence developed and gradually increased until his death some 18 months later. *Rickettsia burneti* was isolated from his bloodstream at the beginning of the chronic febrile illness and again just before death; it was also shown to be present in large numbers in aortic valve vegetations collected after death.

Evans, Powell, and Burrell (1959) have also reported the isolation of *R. burneti* from the aortic valve vegetations and from the spleen of a patient dying five months after an influenza-like illness.

Although subacute rickettsial endocarditis is probably a rare sequel to an acute infection with *R. burneti*, it seemed desirable to examine a number of cardiac patients for rickettsial antibodies so as to obtain an estimate of its frequency.

This paper describes the results of these examinations so far, together with the clinical state, history, and laboratory diagnosis of another patient with subacute Q fever endocarditis who was detected as a result.

Selection of Patients and Methods

Sera were obtained from suspected cases of subacute endocarditis in Leeds and certain other centres. The sera were tested for complement-fixing antibodies to the phase 1 and 2 antigens of *R. burneti* (see Andrews and Marmion, 1959), and also for those against murine typhus and rickettsial-pox group-specific antigens. The complement-fixation test used was either that described by Stoker, Page, and Marmion (1955) or a locally developed micro-method using essentially the same reagent concentrations and incubation times.

Results

Fifty-six patients were tested in the period between April and December, 1959. A diagnosis of subacute bacterial endocarditis, with isolation of *Streptococcus viridans*, enterococci, or other bacteria, was made in 13 of the patients. In 35 of the remainder there was evidence of valvular damage and a strong suspicion of an infective process, but blood cultures were sterile. The remaining eight patients had valvular damage but no evidence of infection.

No patient had C.F. antibody to the group-specific typhus antigen. One patient had Q fever C.F. antibodies and a case report is given below.

Another patient had a C.F. antibody titre of 1/128 to rickettsial-pox group-specific antigen (Lederle). Dr. J. Colquhoun (Department of Bacteriology, Royal Infirmary, Sheffield) kindly informed us about his investigations, which indicate that this patient's endocarditis was of bacteriological origin. No antigenic relationship was shown between the causative bacterium and the rickettsial-pox antigen, and it seems probable that the rickettsial-pox antibody resulted from some past experience. Dr. C. C. Shepard (Montgomery, Ala.) kindly confirmed the specificity of the serological findings by C.F. tests with their rickettsial-pox antigen and by staining smears of *Rickettsia akari* with 1/10 and 1/100 dilutions of the patient's serum, using the indirect fluorescent antibody technique. The patient has not been out of the country, and local investigations into the possible presence of a member of the spotted-fever

group of rickettsiae—or some other organism with a related antigen—are in progress.

Case Report

The patient with Q fever antibody was a window-cleaner aged 48, and was first admitted to hospital (St. Luke's Hospital, Bradford) on June 18, 1957. On the day before admission he had a frontal headache for about three hours, and had sweated a lot and taken plentiful fluids. During the night he shivered and slept fitfully. On rising he noticed weakness of the right arm and leg, together with pain on the left side of his neck. A slight frontal headache was still present.

His medical history revealed that in 1953 he had suffered from an iridocyclitis of the right eye accompanied by extensive retinal haemorrhages and secondary optic atrophy (diagnosed as Eales's disease). At that time the urine was free from albumin and the Kahn reaction was negative, but a chest *x*-ray examination had revealed some cardiac enlargement. His blood-pressure was then 140/60 mm. Hg, but no observations were made on the presence or absence of cardiac murmurs. There was no history of chorea or acute rheumatism. His general practitioner recorded attacks of right-sided pain (? pleurisy) at the age of 23 and again at the age of 41. The family history was not significant except that his elder brother had an attack of chorea at the age of 10 and was known to have had mitral stenosis and aortic incompetence without infective endocarditis at the age of 44. He died in congestive heart failure five years later.

On examination the patient was afebrile and drowsy, but was able to give a coherent history. He had a spastic right hemiparesis without sensory loss. The heart was in regular rhythm with no murmurs and was apparently of normal size. Blood-pressure was 125/65 mm. Hg. The pulsation in the left carotid artery was diminished. He appeared to be anaemic. A lumbar puncture yielded a clear fluid not under increased pressure, with normal chemical readings and with no excess of cells.

During the first few days after admission the patient's drowsiness and the right-sided weakness increased and he became incontinent of urine. A provisional diagnosis of left carotid occlusion was made.

Numerous rhonchi were found in the chest, but, apart from a few temperature recordings of 99° and 99.6° F. (37.2 and 37.6° C.), he was afebrile. A chest *x*-ray film taken with portable *x*-ray equipment gave a poor result but suggested pneumonic changes at the right base. Between June 19 and 24 he was given seven million units of penicillin. He gradually improved except for an unexplained effusion into the right knee-joint on August 17, and he was discharged home in November, 1957. By April, 1958, he was able to do light work in a bakery.

In October, 1958—some 16 months after the first admission—he had several right-sided convulsions and was readmitted to St. Luke's Hospital. He was afebrile. Finger-clubbing was present and the heart was enlarged. An aortic diastolic murmur was now audible at the left sternal edge. No mitral murmurs were detected, but radiological screening revealed a large left auricle.

Investigations revealed a normochromic anaemia and an increased sedimentation rate (57 mm./hour Wintrobe). The urine contained a trace of albumin and there were numerous red cells in the centrifuged deposit. Four blood cultures were sterile and the patient was consistently afebrile. Other negative investigations included examination of the peripheral blood and marrow preparations for L.E. cells, estimation of total proteins and albumin/globulin ratio, a muscle biopsy, and eosinophil counts.

Nevertheless the clinical evidence for infective endocarditis was strong enough to justify antibiotic therapy, and during the next six weeks he was given one million units of penicillin six-hourly.

He failed to improve, and the albuminuria, the anaemia, and the raised sedimentation rate persisted. After six weeks' treatment, prednisone, 10 mg. daily, was substituted for antibiotics, and was continued until mid-February, 1959, without objective evidence of improvement. This steroid was eventually discontinued when the patient developed oedema of the ankles.

In May, 1959, he was transferred to the General Infirmary at Leeds, under the care of Dr. D. Taverner, for further investigation. At this stage he was in congestive heart failure, with auricular fibrillation and unmistakable evidence of both mitral stenosis and aortic incompetence. Inequality of carotid pulsation was confirmed, but there was neither splenomegaly nor evidence of emboli. The urine contained albumin varying in amount from 2 to 5 g./litre. Further investigations revealed a serum albumin of 1.8 g./100 ml., globulin 3.5 g./100 ml., and serum cholesterol of 290 mg./100 ml. Although his cardiac failure responded to digitalis and diuretics his nephrotic manifestations persisted. A biopsy of right and left kidneys in June, 1959, was reported (Dr. C. K. Anderson) as showing the changes of chronic lobular glomerulonephritis (Ellis type 2)—an unusual feature, although it has been described in subacute bacterial endocarditis (Kark *et al.*, 1958; Spain and King, 1952).

During the course of six weeks in hospital the patient was afebrile save on two occasions when temperatures of 99 and 101°F. (37.2 and 38.3°C.) were recorded. Six further blood cultures were sterile, and renewed search for evidence of polyarteritis nodosa or disseminated lupus erythematosus was unrewarded.

As part of the survey of endocarditis patients a sample of serum was then examined for Q fever antibodies and found to be positive.

The patient suffered progressive renal impairment, the blood urea rising to 100 mg./100 ml. He was subsequently transferred to Scotton Banks Sanatorium, where he gradually deteriorated, dying of congestive heart failure on August 26, 1959.

Pathological Investigations

At necropsy significant internal findings were confined to the chest and abdomen. Approximately 2 pints (1,140 ml.) of serous fluid was present in each pleural cavity.

Both lungs were oedematous and the left lung was collapsed, fibrosed, and covered with a layer of fibrous tissue which partially obliterated the left pleural cavity.

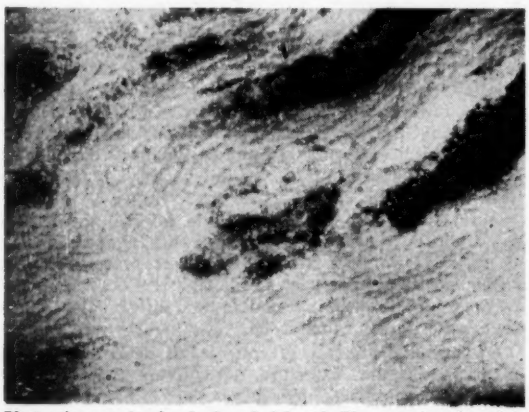
The heart showed moderate hypertrophy and dilation of the right ventricle and gross hypertrophy of the left ventricle. Pulmonary and tricuspid valves were normal but the aortic and mitral valves showed thickening and fusion of the cusps and small nodules of collagen—probably healed vegetations—along their points of opposition. The mitral valve was the more obviously diseased, and in addition to incompetence there was a mild subvalvular type of stenosis due to fibrosis and adhesion of the tips of the papillary muscles with the valve cusps. There was also a small haemorrhagic friable area at the point where the anterior mitral cusp fused with the papillary muscles; possibly a more active vegetation.

In the abdominal cavity there was gross ascites. The liver was slightly enlarged, with a typical chronic congestive ("nutmeg") appearance. No striking abnormality was found in the other abdominal organs, and, in particular, there was no sign of old embolic episodes. There were no significant changes in the brain, in the meninges, or in any other system.

The cause of death was thought to be congestive heart failure due to mitral and aortic valvular disease with healed infective endocarditis.

Histological Investigations

In the anterior mitral cusp there was evidence of a chronic lesion which had largely healed. The deeper parts of the cusp consisted of dense collagen with a very scanty cellular infiltrate of lymphocytes and plasma cells. Among this tissue there were two localized areas which in a haematoxylin- and eosin-stained section appeared to consist of compact masses of basophilic debris. In sections stained by the Giemsa method these aggregations were seen to be collections of rickettsia-like organisms (see Fig.). The microcolonies were elongated, and were composed of numerous organisms 0.5μ or less in size and staining blue-purple with the Giemsa method and a faint red with Gram's stain. As with the case described



Photomicrograph of colonies of rickettsia-like organism found in mitral valve. (Giemsa. ×1,000.)

by Andrews and Marmion (1959), they were not clearly inside or associated with cells. They were closely invested by the collagen and there was little or no inflammatory response in the immediately surrounding tissue.

More superficially in the cusp there were patchy layers of loose granulation tissue in which the mononuclear cellular reaction was more intense. No colonies of bacteria could be identified in these areas, using Giemsa or Gram stains. A small number of cells with cytoplasmic granules varying in size from 0.5 to 2μ or more and staining purple with Giemsa was seen in this area. These were thought to be mast cells rather than cells with intracytoplasmic colonies of rickettsiae. The posterior mitral cusp and the aortic valve, although scarred, showed no signs of active disease and organisms were not seen.

Sections from the lower lobe of the left lung confirmed the macroscopic appearances of old collapse and fibrosis, and there was widespread intra-alveolar oedema and accumulations of "heart-failure" macrophages. No micro-organisms were seen in numerous Giemsa-stained sections. The liver showed chronic venous congestion and the splenic pulp was congested with reactive hyperplasia. Sections from the brain, and mediastinal and mesenteric lymph nodes were normal. Sections of the kidney showed a chronic nephritis (Ellis type 2) and there was no evidence of focal embolic nephritis.

Bacteriological Investigations

Tests on Specimens Taken During Life.—The first positive Q fever complement-fixation finding was obtained with a serum specimen collected on May 11, 1959—that is, about three and a half months before death. There was an antibody titre of 1/256 to the phase 1 C.F. antigen of *R. burneti* and a titre of 1/64 to the phase 2 antigen. Essentially the same titres were obtained in tests carried out on sera collected on May 21 and June 6, 1959. Attempts were made to isolate *R. burneti* from seven samples of heparinized blood (or blood clots) and three samples of urine taken at intervals during May and June but without success.

Tests on Specimens Taken at Necropsy.—Specimens of the lung, liver, kidney, spleen, brain, mediastinal and mesenteric lymph nodes, and the mitral and aortic valves were collected. Bacteriological culture of all these yielded a mixed growth of *Proteus* and an enterococcus—probably post-mortem contaminants. Ten per cent. (w/v) suspensions of the specimens were prepared and 2-ml. quantities were inoculated into guinea-pigs by the intraperitoneal route—two guinea-pigs each for the lung, liver, kidney, spleen, lymph nodes, and brain specimens, and four guinea-pigs each for the aortic- and mitral-valve suspensions. The rectal temperatures of the guinea-pigs inoculated with the heart-valve suspensions were taken daily, and two animals in each group which showed slight elevations of temperature between the 12th and 20th days after inoculation were killed and suspensions of their spleens passed to fresh guinea-pigs. These animals ("second-passage animals") and all those inoculated directly with the specimens ("first-passage animals"), were tested for Q fever C.F. antibody (phase 2) five to seven weeks after inoculation. The guinea-pigs inoculated with lung, liver, kidney, spleen, brain, lymph nodes, and aortic valve were negative. However, one out of two of the second-passage animals in the series inoculated with the mitral-valve suspension had Q fever (phase 2) C.F. antibody at a titre of 1/512. The first-passage animals and the serologically negative second-passage animal in this series were then challenged with known positive material in the manner of Derrick (1937). They did not become febrile, and so appeared to be immune even though they had not developed C.F. antibody.

Consequently a fresh suspension of the mitral valve was prepared and inoculated into eight guinea-pigs and four hamsters. Four of the guinea-pigs were given cortisone acetate, 12.5 mg. subcutaneously, just before the inoculation of the specimen and the same dose 10 and 20 days after inoculation. One cortisone-treated guinea-pig died 25 days after inoculation, and a suspension of its liver and spleen was passed to fresh guinea-pigs. The surviving animals were tested for Q fever antibody four to five weeks after inoculation. The accompanying Table shows the results

Results of Serological Examination of Guinea-pigs and Hamsters Inoculated with a Suspension of the Mitral Valve

Animal	No.	Reciprocal of Titre of C.F. Antibody to the Nine Mile (phase 2) Antigen of *R. burneti*	
		Pre-inoculation Serum	Post-inoculation Serum
Guinea-pigs:			
No cortisone	132	<4	32
	133	<4	64
	134	<4	64
	135	Anti-complementary	32
Cortisone-treated	136	<4	Not tested*
	137	<4	32
	140	<4	64
	141	<4	16
Hamsters	63	Not tested	32
	64	"	64
	65	"	64
	66	"	32

* Died 25 days after inoculation: a suspension of liver and spleen produced Q fever infection in two other guinea-pigs.

obtained, and it is evident that all animals were infected with *R. burneti* and that the rickettsia had been isolated once more from the mitral valve.

Discussion

It seems from the results so far that rickettsial infection, in particular with *R. burneti*, is a rare cause of subacute infective endocarditis—at least in the areas surveyed. If both a pre-existing valvular disease and a Q fever infection are required, then obviously their coincidence in one patient will be rare indeed.

The sequence of events in our present case is not as clear as that observed in the case at the Middlesex Hospital—largely because the serological diagnosis was made only three and a half months before death and at a time when the infection was no longer active. *R. burneti* was isolated from the mitral valve—and no other organ—and rickettsia-like organisms were seen in the valve. It is of some interest that there was no typical attack of Q fever in the patient's history. The hemiplegia in 1957 seems to have resulted from a left carotid occlusion which presumably was either thrombotic or embolic in origin. If the former, then the episode may have been an atypical attack of Q fever. The headache, sweating, and ill-defined signs in the chest would fit with this, and thrombosis of peripheral vessels has been described in Q fever (for discussion and references see Robson and Shimmin, 1959). On the other hand, if the episode was embolic then the cardiac lesion may have existed before 1957, even though there was no detectable evidence of valvular disease at that time.

Despite the absence of a history of rheumatic illness the heart did appear to be enlarged on *x*-ray examination in 1953–4 and occasional blood-pressure readings had always revealed a wide pulse pressure. These findings, coupled with the occurrence of the fatal rheumatic heart disease without evidence of subacute infective endocarditis in the patient's brother, raise the suspicion of a silent rheumatic carditis in early life subsequently aggravated by a later and superimposed Q fever endocarditis.

After the hemiplegic attack, and during the subsequent two years of chronic illness, the picture was one of subacute infective endocarditis with the development and increase of cardiac murmurs, anaemia, and finger-clubbing, with, however, little or no fever. Repeated blood cultures in several hospitals were sterile and several courses of penicillin were ineffective.

A diagnosis of Q fever infection would not have been made but for the routine serological testing. It is suggested, therefore, that a Q fever complement-fixation test might well be done as a routine on patients with suspected subacute infective endocarditis —especially when there is a sterile blood culture, or no response to penicillin, or when treatment with corticosteroids is to be given.

It is of particular interest that the patient's serum, unlike that of an uncomplicated case of Q fever, contained antibody against the phase 1 C.F. antigen of *R. burneti*. This finding reinforces the suggestion (Andrews and Marmion, 1959) that the presence of phase 1 C.F. antibody may be a useful indicator of chronic Q fever, but obviously more cases will have to be examined before a firm conclusion can be reached.* In this connexion it may be noted that the sera from the patient described by Evans *et al.* (1959), when tested in Leeds, did not contain antibody against phase 1 C.F. antigen. This and some other differing features may perhaps be the result of the relatively short period—five months—between the presumptive attack of Q fever and death in their patient.

*Since this paper was completed Dr. N. R. Grist (Glasgow) has told us about another case of Q fever endocarditis, and we are also investigating one seen by Dr. Louis Glick (Halifax General Hospital). Both patients had high titres of antibody to Phase 1 antigen.

Summary

A small series of patients with suspected or proved subacute infective endocarditis have been examined for Q fever, murine typhus, and rickettsial-pox complement-fixing antibodies.

The results indicate that subacute rickettsial endocarditis is not a numerically important cause of the syndrome of subacute infective endocarditis with a sterile blood culture.

Fifty-six patients were examined. None had typhus C.F. antibody. One had rickettsial-pox C.F. antibody, a finding unconnected with his endocarditis. Another had Q fever antibody and was found to have a healed Q fever endocarditis.

The last patient, a middle-aged man with aortic- and mitral-valve disease, had symptoms and signs suggesting subacute infective endocarditis for over a year before his death. *R. burneti* was isolated from the mitral valve after death and rickettsia-like organisms were seen in sections of the valve.

C.F. antibody to the phase 1 antigen of *R. burneti* was again demonstrated, and a wider use of the Q fever complement-fixation test in the investigation of subacute infective endocarditis is suggested.

We are indebted to the following persons for permitting and arranging the collection of specimens from the cardiac patients. Professor C. L. Oakley and the staff of the department of bacteriology, University of Leeds; the consultant physicians of the General Infirmary at Leeds; Dr. W. Goldie and the staff of the department of pathology and the consultant physicians at St. James's Hospital, Leeds. Thanks are also due to physicians and pathologists in various parts of the country who sent sera from their patients. In particular we are grateful to Dr. D. Taverner for his help and for allowing us to publish details of the patient with Q fever who was under his care. We are also grateful to Dr. L. Smith (Bradford), Dr. R. K. MacCuish (St. Luke's Hospital, Bradford), and Dr. K. M. Barran (Scotton Banks Sanatorium) for information about the patient. Dr. C. C. Shepard (Communicable Disease Centre, Montgomery, Ala.) gave much help with advice, rickettsial-pox antigens, control sera, and confirmatory tests. Dr. H. R. Cox (Lederle), Dr. D. Lackman (Rocky Mountain Laboratory, Montana), and Dr. J. Tonge (Brisbane) also kindly provided certain antigens and control sera.

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The Reticuloendothelial Society (New England Institute for Medical Research, Ridgefield, Connecticut, U.S.A.) will shortly be publishing a symposium entitled "Reticuloendothelial Structure and Function." Investigators who live outside the United States may claim a 20% discount on the volume, provided they have an academic affiliation and the order is placed through the institution to which they belong.

PROTECTION OF MICE AGAINST THE LETHAL ACTION OF AN ENCEPHALITIS VIRUS

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Although interferon was first found (Isaacs and Lindenmann, 1957) in the course of investigating a laboratory phenomenon, virus interference, subsequent investigations have brought it nearer to virus infections of man. In the first place, interferon has been shown to protect cells *in vitro* against infection with a wide range of viruses, and in one instance—namely, vaccinial infection of the rabbit skin—protection was found *in vivo* also (Isaacs and Westwood, 1959). In the second place, production of interferon has been shown to be a response of many different kinds of cells to infection with a variety of different viruses *in vitro* and *in vivo*, and there is some evidence that both *in vitro* (Ho and Enders, 1959; Henle *et al.*, 1959) and in the animal body (Isaacs and Hitchcock, 1960) production of interferon may have a protective action against virus infection.

If we consider interferon as a protective response of cells to virus infection we can usefully compare it to the production of specific antibody. The antibody response to infection has been exploited in medicine in two different ways. Antibody may be given *passively*—that is, antibody produced in one animal or individual is administered to protect a second animal or individual. Alternatively, an animal or individual may be stimulated *actively* to produce antibody needed for its own protection. By analogy one could imagine that interferon might be used to protect after passive administration, or by actively stimulating an animal to produce enough interferon to protect itself.

In the present experiments mice have been protected against the lethal action of an encephalitis virus (Bunyamwera virus) both by passive administration of interferon and by actively stimulating the mice to produce interferon. The degree of protection achieved has not been great, though it is statistically highly significant. But, in spite of the low degree of protection achieved, the results are reported now, since they emphasize a principle which may be useful in future experimental work.

Preparation of Interferon

In Tissue Culture.—8-oz. (225-ml.) medical flat bottles containing thick sheets of about one-week-old primary mouse embryo fibroblasts were infected with the Kunz strain of influenza A^1 virus diluted 10^{-2} in 12 ml. of Parker's 199 medium. After incubation for three or five days at 37° C. the medium was harvested and dialysed against HCl/KCl buffer at *p*H 2 for 12 hours at 4° C. to kill the virus. It was then brought back to *p*H 7.4 by dialysis against two changes of Earle's buffered salt solution at 4° C. This fluid was used as such or after concentration 5 to 10 times by pressure dialysis. Control fluid was made in the same way without addition of virus.

In Mouse Lungs.—Swiss white mice (TO strain) of ages varying from 3 to 8 weeks were inoculated intranasally under light anaesthesia with 0.05 ml. of the PR 8 strain of influenza virus A diluted 10^{-5} in broth saline and containing about 600 egg infective doses of virus. After three days the mice were killed with coal-gas and their lungs removed and ground up in 1 ml. of Earle's saline to each pair of lungs. After centrifuging, the lung extracts were treated at *p*H 2, as described for tissue-culture interferon. Ten times concentration of lung extracts was accomplished by negative-pressure ultrafiltration. Control extracts were made from normal mouse lungs.

Mouse Protection Experiments

TO mice (about 3 weeks old and weighing 10–12 g.) were used in all experiments, and caged in groups of six.

Protection by Interferon Given Intraperitoneally.—Doses of 0.2 ml. of interferon or control material were inoculated intraperitoneally on two consecutive days. The mice were also challenged on the second day with 0.2 ml. of Bunyamwera virus intraperitoneally. A stock of Bunyamwera virus made in baby mouse brains and stored at −79° C. was used in all experiments. A range of $\log_{10}$ dilutions of virus was used in every experiment in both the control and the interferon-treated mice. In assessing the results, the dilutions of virus which killed 50 to 100% of control mice were picked and the numbers of mice killed by these dilutions in the two groups were compared. A record was kept of the day of death of the mice, and the mean day of death after challenge was calculated for each group.

Protection by Influenza Virus Given Intranasally.—Pools of Kunz strain of influenza virus A were made from embryonated eggs infected by the allantoic route. Infected allantoic fluid was diluted 1/10 in broth-saline and 0.05 ml. inoculated intranasally in mice under ether anaesthesia. This dose contains 10^6 to 10^7 egg infective doses of virus. Control mice were not inoculated. All mice were challenged with Bunyamwera virus as described above and the results assessed in the same way. The influenza virus was given at various days before and after the challenge virus. The Kunz virus did not kill mice when given intranasally at this dosage, but usually the mice became sick two days after inoculation, and, if killed, they could be seen to have influenzal lung lesions. They recovered from this infection by the sixth day.

Results

Protection of Mice by Intraperitoneal Inoculation of Interferon

Table I shows the combined results of 11 experiments carried out in an effort to protect mice against encephalitis by the Bunyamwera virus. Mouse-tissue-culture interferon was used in three experiments and

TABLE I.—*Protection of Mice by Intraperitoneal Inoculation of Interferon Prepared in Tissue Culture and in Mouse Lungs*

Interferon Prepared in	No. of Mice Dead after Intraperitoneal Challenge with Bunyamwera Virus		
	Control	Interferon-treated	p
Tissue culture (3 experiments)	21/36	8/37	<0·01
Infected mouse lungs (8 experiments)	69/90	27/72	<0·01
Total (11 experiments)	90/126	35/109	<0·01

mouse-lung interferon in eight experiments. The combined results of all 11 experiments are shown, and this degree of protection is highly significant at the 1% level.

The average difference between the LD_{50} (50% lethal dose) of interferon-treated and control mice was $\log_{10}$ 1.0 over five experiments—that is, the interferon treatment reduced the effective lethal dose of virus by a factor of 10 times.

An attempt was also made to see whether interferon would protect mice against challenge by Bunyamwera virus inoculated intracerebrally. This is a much more severe test of resistance, and no protective effect was found in these experiments.

Protection of Mice by Infection with Avirulent Influenza Virus

It has been previously reported that interferon is demonstrable in the lungs of mice after infection with either a small dose of virulent influenza virus or a large dose of avirulent virus. In mice infected in this way the concentration of interferon in the lungs remained high in the first few days of infection but was lower on the seventh day (Isaacs and Hitchcock, 1960). The possibility was considered that interferon, produced in the lungs, might pass into the blood-stream and spread to other tissues and organs. Accordingly, experiments were designed (as described above) to see whether a large dose of influenza virus, which produced interferon in the lungs, would protect mice against intraperitoneal challenge with Bunyamwera virus.

TABLE II.—*Protection of Mice by Intranasal Inoculation of Avirulent Influenza Virus*

Influenza Virus Inoculated Intranasally	Deaths from Intraperitoneal Challenge with Bunyamwera Virus	
	No. of Mice Dead	Mean Day of Death
One day before challenge ..	1/12	9
Day of challenge	6/12	8·5
One day after challenge ..	3/12	7·7
Two days " " ..	7/12	10
Nil	10/12	7·6

Table II shows the results of one experiment. These suggest that the influenza virus infection protected the mice when it was given one day before, along with, or one day after the challenge virus.

The mean day of death for the mice which died in the various groups is also shown in Table II. It can be seen that influenza virus infection reduced the number of deaths and delayed the day of death. The pooled results of three experiments, shown in Table III, indicate that influenza virus given one day before challenge induced statistically significant protection in these experiments. Influenza virus given after challenge did not reduce significantly the numbers of deaths in further experiments, but a slight protective effect was indicated by delay in the day of death. Similar experiments were then carried out except that the mice were challenged with Bunyamwera virus by the intracerebral route, but no protective effect could be shown. One experiment was also carried out to see whether a combination of passive inoculation of interferon and active infection with influenza virus would produce greater protection than either separately, but no additive effect was found.

Mice known to be producing interferon in their lungs as a response to influenza virus infection were killed at intervals and an attempt was made to detect influenza virus and interferon in the blood-stream and interferon in the brains. At no time was any trace of viraemia found, a result which is in agreement with present knowledge of the pathogenesis of influenza. In one experiment a small amount of interferon was demonstrated in both serum and brains at about three days after infection, but in other experiments interferon could not be demonstrated. It appears that if interferon is liberated into the blood-stream it is present there only in small amounts.

TABLE III.—*Protection of Mice by Intranasal Inoculation of Avirulent Influenza Virus (Pooled Results of Three Experiments)*

Influenza Virus Inoculated Intranasally	Deaths from Intraperitoneal Challenge with Bunyamwera Virus	
	No. of Mice Dead	Mean Day of Death
Day before challenge ..	10/20	8·5
No influenza virus given ..	31/36	7·0
	$p<0.01$	

14 to 21 days after virus challenge, sera were collected from mice protected by interferon and tested by the technique of Porterfield (1960) to see if they contained antibodies to Bunyamwera virus. In a proportion of animals which recovered, viral antibody was detected in their sera. Further investigations are required on the course of development of antibody in these animals.

Discussion

These experiments have had the very limited aim of trying to see whether it is possible to protect animals against a systemic virus infection by passive administration of interferon and by active stimulation of interferon production. Slight but definite protection has been achieved by both methods, but so far only very limited experiments have been carried out to see whether different dosages and different schedules of administration of interferon would increase the degree of protection.

In addition, little is known of the method by which interferon confers increased resistance in mice. Its antiviral action is probably short-lived, and yet virtually complete protection is achieved in individual animals. This suggests that passively administered interferon inhibits virus growth without inhibiting the natural defences of the body. The natural defences would include production by the infected animal of fresh interferon and antibody. There is already evidence that interferon, in doses which inhibit virus growth, does not inhibit the production of fresh interferon *in vitro* (Isaacs and Burke, 1958). It is not yet known whether interferon affects antibody production, but the finding of viral antibody in mice which had been treated with interferon, infected with encephalitis virus, and which then recovered, is encouraging. It therefore appears that in this situation the interferon acted by limiting the number of cells which would support virus growth, and thus it slowed down the rate of virus multiplication sufficiently to allow time for mobilizing the natural defences of the body.

It was surprising to find that influenzal infection of mice could protect them against an encephalitic infection. Viral interference has, of course, been a well-recognized phenomenon from the time that Findlay and MacCallum (1937) showed that monkeys infected with Rift Valley fever virus were temporarily resistant to the virulent yellow-fever virus, these two viruses being antigenically unrelated. Many similar examples have

been described since then, but it had usually been assumed that the interference was due to occupation of cells by the first virus, leading to exclusion of the second virus. The interest of the present experiments is that the influenza virus remains in the lungs and cannot be demonstrated in the blood-stream, so that the resistance of the mice is probably due to interferon produced in the lungs and diffusing to the other organs via the blood-stream. An analogous explanation has been put forward to account for the observation of Burnet and Fraser (1952) that chick embryos infected with influenza virus in the allantoic cavity became resistant to the lethal action of the neurotropic influenza virus strain NWS. Grossberg, Hook, and Wagner (1960) found that a similar resistance could be induced by inoculating interferon into the allantoic cavity, and they suggested that the "interference at a distance" described by Burnet and Fraser was due to the production of interferon in the allantoic cavity as a result of infection with the influenza virus, followed by diffusion of the interferon into the chick embryo.

The present experiments do not allow us to tell which would be the best route towards the goal of protecting man against virus infections, but they point to a number of interesting avenues of exploration.

Summary

Mice were protected to a slight but statistically highly significant extent against the lethal action of an encephalitis virus. Two different methods were used. The first was by intraperitoneal inoculation of interferon, and the second by active infection with influenza virus. The influenza virus grows in the mouse lung and protects the mice apparently by inducing production in the animals' lungs of interferon, which then diffuses into the blood-stream. It is suggested that interferon may protect the mice by inhibiting the growth of the encephalitis virus without impairing the animals' natural bodily defences.

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Four times as many overseas students as there were 10 years ago are now in Britain. The estimated total for 1959–60 is 47,500. More than half were living and studying in the London area. These and other facts are contained in a new and expanded edition of a handbook, *Overseas Students in Britain*, published by the Standing Committee of the London Conference on Overseas Students, which represents about 70 organizations concerned with overseas students and has a secretariat provided by the British Council. The booklet may be obtained from the London Overseas Department of the British Council, 3 Hanover Street W.1. (Price 1s. 6d., post free.)

STUDIES WITH ^{131}I TRIOLEIN IN SOUTH AFRICAN BANTU AND WHITE SUBJECTS, AND IN PATIENTS WITH MYOCARDIAL INFARCTION*

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Recent studies on the levels of blood radioactivity after the oral administration of ^{131}I triolein have demonstrated significant differences between normal subjects and patients with ischaemic heart disease (Likoff *et al.*, 1958; Seller *et al.*, 1959). Likoff *et al.* estimated the radioactivity in whole blood and in the trichloracetic acid precipitable fraction after the oral administration of ^{131}I triolein to normal males and to males who had suffered a previous myocardial infarction. Significant differences in radioactivity at the peak time and at the 24-hour interval were demonstrated in the two groups. In a similar study, Seller *et al.* found the blood radioactivity of normal subjects after the oral administration of ^{131}I triolein to be much lower than in patients with ischaemic heart disease.

Plasma levels of radioactivity after the oral administration of ^{131}I triolein probably represent a complex resultant of the rates of fat absorption from the bowel and of clearance from the blood. The results in ischaemic heart disease and control subjects would therefore appear to reflect metabolic differences in regard to one or the other mechanism, or to both.

There are well-recognized differences in the dietary and disease patterns in the South African White and Bantu populations. While the consumption of fat and the incidence of ischaemic heart disease in Whites are probably comparable to those of the people of Western Europe and the United States, the average Bantu diet contains little fat (Walker and Arvidsson, 1954), and myocardial infarction is rare. Although this rare incidence of ischaemic heart disease among the South African Bantu may be a reflection of constitutional differences, habitual dietary factors, especially the type and amount of fat consumed, may also be of significance.

Material and Methods

In the present study the absorption and plasma clearance of a test dose of ^{131}I triolein was followed in Bantu and White subjects having no evidence of ischaemic heart disease, and in White patients convalescing from an attack of myocardial infarction.

Bantu Subjects.—29 male hospital patients aged 40 to 60, convalescing from diseases not generally affecting absorption from the gastro-intestinal tract, and with no evidence of ischaemic heart disease.

White Control Subjects.—30 male hospital patients aged 40 to 60. There was no evidence of any disease affecting gastro-intestinal absorption, or ischaemic heart disease.

*This study was made possible by a grant from the Atomic Energy Board, Pretoria, South Africa.

Myocardial Infarction.—20 white males aged 40 to 60, convalescing from a recent attack of myocardial infarction, diagnosed by the characteristic clinical picture and electrocardiographic changes.

^{131}I triolein obtained from the Radiochemical Centre, Amersham, England, was diluted with olive oil to a concentration of 50 μc./10 ml. The 50-μc. dose, together with 50 ml. of milk, was given orally to the patient in the fasting state. Part of the milk was used to rinse out the container, and the rinsings were administered. Residual radioactivity in the container was negligible on assay. After receiving the dose the patient was permitted the usual hospital breakfast, and there were no further dietary restrictions during the test period. Thyroid uptake of ^{131}I was blocked by administering three drops of Lugol's iodine three times on the day prior to the test, and a further three drops together with the test dose of ^{131}I triolein. Venous blood was withdrawn at 4, 6, 8, 12, 24, and 36 hours after administration of the test dose, and placed in heparinized containers. The radioactivity of 3–5 ml. samples of plasma was determined in a well-type scintillation counter containing a thallium-activated sodium iodide crystal. The counting-time varied with the activity of the sample, but all samples were counted to within at least 2% accuracy. With each batch of ^{131}I triolein used, part of the solution was retained as a standard, a dilution of which was counted with each assay of plasma radioactivity. This obviated the necessity for corrections for radioactive decay. The percentage of administered radioactivity per 1,000 ml. of plasma was calculated.

Results

The mean percentages of administered radioactivity absorbed per litre of plasma in the three groups at different time intervals after the dose was fed are shown in Table I and are presented graphically in the Chart. Table II shows the percentage of subjects reaching their maximum percentage absorption before and after four hours.

TABLE I.—*Plasma Radioactivity after Administration of ^{131}I Triolein to Bantu and White Control Subjects, and to Patients with Myocardial Infarction.*

Group	No. of Subjects		Percentage of Administered Radioactivity per Litre Plasma					
			4 hrs.	6 hrs.	8 hrs.	12 hrs.	24 hrs.	36 hrs.
Bantu	29	Mean	2·94	2·64	2·58	1·86	1·16	0·60*
		S.D.	1·6	0·9	0·7	0·5	0·5	0·3
White controls	30	Mean	3·16	3·38	2·88	1·92	1·04	0·40
		S.D.	1·7	1·5	1·4	1·1	0·6	0·3
Myocardial infarction	20	Mean	3·90	4·14	3·32	2·28	1·22	0·54
		S.D.	1·9	1·8	1·1	0·9	0·6	0·5

* 21 subjects only.

TABLE II.—*Percentage of Subjects Reaching Their Maximum Percentage Absorption Before and After Four Hours.*

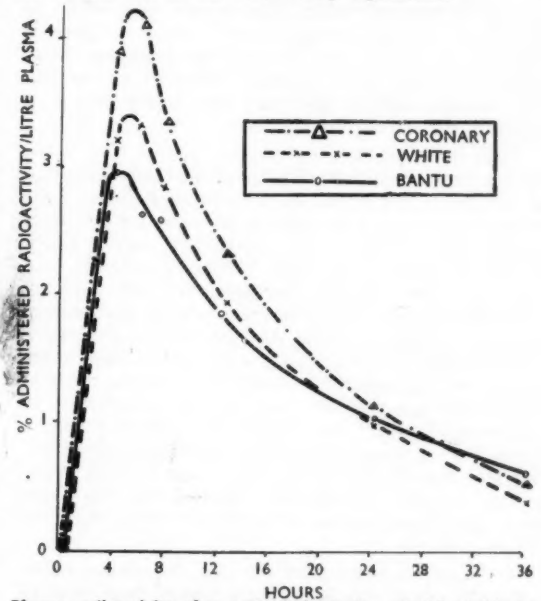
	Before 4 Hours	After 4 Hours
Bantu	58·6%	41·4%
White controls	46·66%	53·33%
Myocardial infarction	50·0%	50·0%

Bantu and White Control Groups.—The mean levels of plasma radioactivity in the Bantu patients were lower than those of the White control group at 4, 6, 8, and 12 hours, but were higher at 24 and 36 hours. Only the differences at 6 hours and 36 hours were statistically significant ($p<0.05$).

White Control and Ischaemic Heart Disease Groups.—The mean levels of plasma radioactivity in the ischaemic heart disease group were higher than those of the control group throughout the 36-hour period of study. The differences, however, were not statistically significant.

Bantu and Ischaemic Heart Disease Groups.—Mean plasma radioactivity in the ischaemic heart disease groups was higher than in the Bantu patients at 4, 6, 8, 12, and 24 hours, but lower at 36 hours. The differences at 6 and 8 hours were statistically significant ($p<0.01$ and at 12 hours $p<0.05$).

Bantu and White Groups.—59% of the Bantu reached their maximum percentage absorption under 4 hours, while for both White groups 46.66 to 53.33% did so. This difference is not statistically significant.



Plasma radioactivity after oral administration of ^{131}I triolein to White and Bantu control subjects, and to patients with myocardial infarction.

Discussion

In the present study the total plasma radioactivity only was assayed, since separate assay of the trichloracetic acid precipitable fraction has been shown to yield little additional information (Likoff *et al.*, 1958; Seller *et al.*, 1959). Activity was expressed per litre of plasma, as this appears to be a more valid index of the concentration of the fat in the blood than that based on a calculated blood volume as an arbitrary percentage of body weight.

Recent studies confirm the validity of metabolic studies with iodinated fat. In dogs, ^{131}I triolein administered intravenously as an emulsion disappears at the same rate as natural fats (Van Handel and Zilversmit, 1958). In view of the great similarity in clearing ^{131}I triolein and the carrier fats of the artificial emulsion, it is unlikely that ^{131}I is removed from the circulation at a rate different from that of the carrier fat.

Bantu and White subjects with and without evidence of ischaemic heart disease showed differences in their plasma radioactivity curves. Although the mean observed peak of the Bantu group was at four hours after the administration of the fat load, that of the White groups was six hours after the load. Examination of the

individual maximum recorded percentage absorption of the subjects, however, does not permit any significance to be attached to these differences, since many subjects in all three groups appeared to reach their maximum before the first reading was taken—that is, before four hours. Furthermore, in some cases, while the highest recorded percentage was at six hours, it was not possible to assess whether the maximum occurred at some time between four and six hours or at some time between six and eight hours. The number of cases in all groups who reached their maximum recorded percentage by four hours, and the numbers that reached the maximum after four hours, have therefore been compared (Table II). While 59% of the Bantu reach the maximum percentage absorption under four hours, only 46.66 to 53.33% of the White groups did so. There is no difference between the White controls and the ischaemic heart disease patients. The 10% racial difference may or may not be real, but on the available sample size it is certainly *not* statistically significant.

While the mean levels of radioactivity of both White groups were significantly higher at six hours than that of the Bantu, the slopes of the ascending parts of the absorption curves were almost identical for all three groups (see Chart). The absorption curves which reflect a resultant of both plasma absorption and clearance rates indicate, therefore, that not only are the initial rates of absorption significantly greater than the rates of clearance, but that the rates of absorption are very similar in all three groups. Differences in the heights of the peaks of absorption, and the times at which they are reached, may thus be a reflection of differences in the rates of clearance. Since the peak values for the Bantu subjects tend to be not only earlier but also significantly lower than those of both White groups, it could therefore be inferred that the Bantu have significantly faster fat-clearance rates than the White subjects.

At 24 and 36 hours after the load, the plasma radioactivity levels of the Bantu were higher than those of the White controls. The reason for this phenomenon is not clear, but may be a further indication of faster clearance rates in the Bantu, since the higher residual levels may be due to earlier feed-back of labelled lipids. In fact, recent studies on the composition of plasma fatty acids during alimentary lipaemia by Dole *et al.* (1959) suggest that the fatty acid pattern of chylomicrons in plasma is stabilized by equilibration with the larger pool of tissue lipids, this constancy of the fatty acid patterns being due to rapid recycling of the lipid components. Faster clearance rates of ^{131}I radioactivity with consequently more rapid equilibration of plasma and tissue lipids would therefore lead to earlier feed-back to labelled lipids, the net result being measurably higher radioactivity levels in the plasma. These higher residual levels in the Bantu may also be the result of liver dysfunction, a possibility at present under investigation.

Since ischaemic heart disease is rare among the Bantu it seems apparent that the absence of ischaemic heart disease may be associated with fast fat-clearance rates, or, conversely, that ischaemic heart disease may be associated with slower (and possibly impaired) fat-clearance rates. If the Bantu could be considered as the true normals, ischaemic heart disease would therefore appear to be partly due to an impaired rate of removal of fat from the plasma, and this would offer a possible explanation for recent findings that ischaemic heart disease is associated with raised fasting serum triglyceride levels (Albrink and Man, 1959; Antonis and Bersohn, 1960).

Summary

Plasma radioactivity over a period of 36 hours after the ingestion of ^{131} triolein has been studied in groups of older (40 to 60 years) Bantu and White subjects without evidence of ischaemic heart disease, and in patients suffering from myocardial infarction.

The Bantu subjects, in whom the intake of animal fat and the incidence of myocardial infarction are both low, show lower initial levels of plasma radioactivity when White subjects with and without ischaemic heart disease, but higher levels at 36 hours. The interpretation of these findings is discussed.

It is suggested that ischaemic heart disease may be partly due to an impaired rate of removal of fat from the plasma.

We thank the Director of the South African Institute for Medical Research for his interest in this study.

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POLIOMYELITIS EPIDEMIC IN MAURITIUS AND THE EFFECT OF VACCINATION

BY

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During June–September, 1959, a poliomyelitis outbreak occurred in Mauritius, 97 paralytic cases being admitted to the Princess Margaret Orthopaedic Centre.

Sporadic cases of poliomyelitis have been known in the island since a recognized outbreak in 1912. The disease became notifiable in 1925. There was a major epidemic in 1945, which was described by Seddon, Hawes, and Raffray (1946) and by McFarlan, Dick, and Seddon (1946). The attack rate in 1945 of about 2 per 1,000 was comparable with the 1916 outbreak in New York and the 1942–3 outbreak in Malta. In 1945, when Seddon, Dick, and McFarlan were in the island, they found a considerable number of old cases—one of them dating from 1891.

Another outbreak lasted from November, 1948, to February, 1949, and another one from March to June, 1952. Since then there have been a few cases every year except in 1957 and 1958, when no cases were notified.

State of Immunity of the Child Population before the Present Outbreak

In 1955 a polio immunity survey was carried out in the island with the assistance of Dr. J. H. S. Gear. The results of the tests made on 80 children under 10 years are shown in Table I.

TABLE I.—*Immunity Survey in Children up to 10 Years*

Age Group	Total	Type 1		Type 2		Type 3	
		+	−	+	−	+	−
1–5	37	21	16	23	14	27	10
6–10	43	35	8	38	5	29	14

In September, 1957, Canadian Salk vaccine was offered to all children aged between 1 and 5 years. In September, 1958, it was offered to all children between 1 and 2 years, and in April, 1959, also to all between 1 and 2 years. The routine was to give the first two injections at an interval of three to four weeks and the third injection after seven months. By the end of June, 1959 (the outbreak started while the vaccination campaign was still on but was nearing its end), (*a*) 43,395 children between 1 and 7 years had received three injections; (*b*) 35,603 children between 1 and 7 years had received two injections; (*c*) 20,330 children between 1 and 7 years had received one injection; and (*d*) 25,790 children between 1 and 7 years had not had the vaccine.

The Present Outbreak

The outbreak began on June 13, 1959. The first patient—a male child, aged 21 months, who had not had Salk vaccine—was admitted to hospital from the rural district of Pamplemousses, which is in the north of the island and adjoins the urban district of Port Louis. According to the mother, the child fell ill on June 13 with fever, was well the next day, and paralysis of the left lower limb developed on the 15th—that is, two days later. Previous to that, on May 4, the child was ill with slight fever, vomiting, and diarrhoea (seven or eight motions a day) necessitating admission to the local sugar estate hospital. He was discharged from hospital after eight days, apparently recovered, and, according to the mother, he remained well until the illness on June 13. His sisters, aged 3, 4, and 6 years, had received two injections of Salk vaccine in September–October, 1957, and were apparently well. No other case of illness occurred in the family during that time or the previous few weeks.

The second patient, a male child aged 10 months, was not admitted until July 10, though he had been ill since June 19. He came from Port Louis, the capital town, about 13 miles from the first case. The third patient, a girl aged 3 years, was admitted on June 25, having fallen ill on June 22; she came from the town of Beau Bassin, in the urban district of Plaines Wilhems, six miles from the second case. From then on, until September 12, 97 cases in all were admitted to the Princess Margaret Orthopaedic Centre from various parts of the island. The dates of onset of the illness and the ages of the patients are shown in Table II.

The youngest patient was 5½ months and the oldest 32 years. The number of cases in each of the nine districts is shown in Table III, and the island distribution of the cases is shown in the map.

It will be seen that no area of the country has escaped.

However, all the cases have been isolated individual ones, and no apparent connecting link has been found between them. One town alone (Vacoas), in the urban district of Plaines Wilhems, had 10 cases—that is, 10.3% of the total.

There being no isolation hospital for infectious diseases on the island, all cases were admitted to the orthopaedic centre under the care of the orthopaedic surgeons.

Diagnosis.—Lumbar puncture was done on the first few cases. Also stools and samples of blood from the first nine patients were sent for isolation of virus to Dr. J. H. S. Gear at the Poliomyelitis Research Foundation Laboratories, Johannesburg. Type 1 poliovirus was isolated from all the nine stool specimens; virus was not isolated from the specimens in baby mice.

Clinical Findings

In most cases the signs and/or symptoms at the onset were fever, headache, or pain in the neck, back, or one of the limbs. The majority of cases were mild. Six needed treatment in an iron lung, but only for a maximum of three weeks. There were no deaths. As to

TABLE II.—*Dates of Onset and Ages of Patients*

Date of Onset	No.	Age in Years											
		-6/12	6/12-	1-	2-	3-	4-	5-	6-	7-	8-	9-	10+
June 7–13	1			1									
,, 14–20	1		1										
,, 21–27	1					1							
,, 28–July 4	5		1		4								
July 5–11	10		2	3	3		1						1
,, 12–18	20		2	9	4	1	1	1					2
,, 19–25	17	1	1	7	4	1	1				1		1
,, 26–Aug. 1	22		2	7	7	3		1	2				
Aug. 2–8	6		1	4	1								
,, 9–15	7		1	1	3			1			1		
,, 16–22	4			1		2				1			
,, 23–29	0												
,, 30–Sept. 5	1					1							
Sept. 6–12	2			2									
Total	97	1	11	35	26	9	3	3	2	1	2	0	4

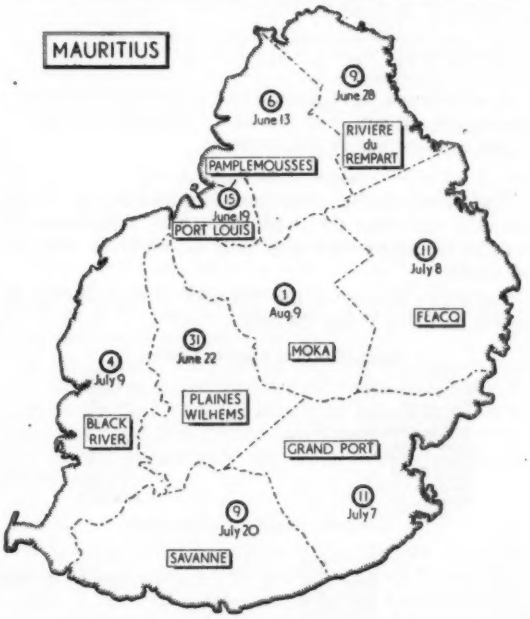

TABLE III.—*Number of Cases by District*

District	Population (June, 1959)	No. of Cases
Port Louis (urban)	105,327	15
Pamplemousses	49,796	6
Riviere du Rempart	52,064	9
Flacq	71,315	11
Grand Port	64,180	11
Savanne	43,599	9
Plaines Wilhems (urban)	184,416	31
Moka	34,003	1
Black River	16,497	4

the site of paralysis, in 77.3% one or both lower limbs were affected, and in 27.9% the upper limb.

It is worth noting that before the outbreak was recognized, and even during the outbreak, errors in early diagnosis were encountered, and in 5 out of 80 cases analysed in detail the first diagnosis was acute appendicitis, acute rheumatism, osteomyelitis, suspected fracture of limb, and enteric fever respectively. These and other cases received injections of antibiotics or vitamins; but later, when paralysis had set in and the diagnosis was obvious, it was found that there was no real relationship between the site of injection and the site of subsequent paralysis.

Epidemiological Findings

A detailed analysis of 80 cases was made. No accurate estimate of the incubation period was possible. Very commonly, the mother of the child noticed only fever a day or two before paralysis set in. Typically, the paralysis was apparent when the fever had subsided and when the child could not use either one of the upper or lower limbs.

In spite of gross overcrowding in the households, and though in most cases before paralysis the patient had been sleeping with either one or both parents and/or with other children, there was not a single multiple case in the family. In the 1945 epidemic 24 multiple cases were seen out of 1,018 cases.

The attack rate in the different ages is shown in Table IV.

TABLE IV.—*Attack Rate by Ages Per* 100,000

0–	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–	11–	15+
55·3	154·2	115·2	41·8	14·8	15·2	10·7	5·6	11·6	0	6·0	0	0·8

It will be seen that there are few adults and adolescents among the patients, and the term "infantile paralysis" is not a misnomer in this outbreak.

Course of the Outbreak

The weekly incidence of cases is shown in Fig. 1. It shows a rise from the third week, with a peak in the seventh to eighth week and with the outbreak over in 14 weeks.

The date of onset of the first case in each district is shown in Table V and the map.

TABLE V.—*First Case in District*

District	Date
Pamplemousses	June 13
Port Louis	,, 19
Plaines Wilhems	,, 22
Riviere du Rempart	,, 28
Grand Port	July 7
Flacq	,, 8
Black River	,, 9
Savanne	,, 20
Moka	August 9

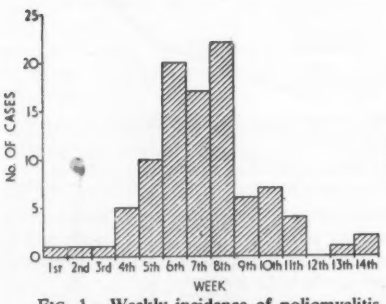

FIG. 1.—Weekly incidence of poliomyelitis outbreak in 1959.

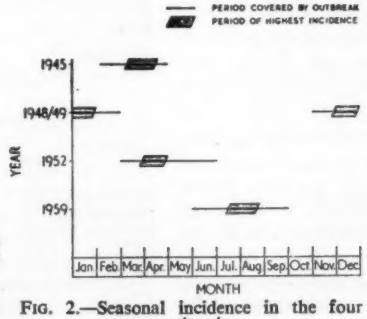

FIG. 2.—Seasonal incidence in the four outbreaks.

It will be seen that the only case in Moka district, in the central part of the island, occurred during the ninth to tenth weeks of the outbreak, and the first case in Savanne district (in the south of the island) occurred during the seventh week.

Preventive Measures

General.—No drastic measures which would increase panic were taken. Schools were not closed. They broke up for the normal August vacation on July 31 and remained closed until September 1. The school holiday camp, at the seaside, situated in the Pamplemousses district and receiving weekly batches of about 200 children aged between 10 and 16 years from all parts of the island, was allowed to run, but was under close medical supervision. The usual advice to avoid over-exertion, games, etc., was given to the public through radio and press. Advice was also given on the avoidance of injections, nose and throat operations, and sports meetings. Personal hygiene was encouraged, and the press and radio announced daily the number of cases notified. This helped to combat rumours.

Vaccination.—On August 14, Dr. P. D. Winter, of the Poliomyelitis Research Foundation, Johannesburg, arrived in the colony with Sabin type 1 poliovirus vaccine. After consultation, the Minister of Health decided upon a vaccination campaign with Sabin vaccine for all children between the ages of 6 months and 10 years. The Health Department opened vaccination centres, each in charge of a medical officer, and vaccination was begun on August 24—that is, 11 weeks after the outbreak started. There was a big response from the public, and in about 10 days some 195,000 children out of an estimated child population of 213,000 received Sabin live attenuated virus type 1.

Before the campaign began, samples of stools and blood from family groups, and blood from children under 6 years who had never received Salk vaccine, were taken at random from all parts of the island for virological studies in Johannesburg.

In all, 510 samples of blood and 202 specimens of stools were obtained before vaccination. Arrangements were made to collect post-vaccination blood and stools, at intervals, from the same individuals.

End of Outbreak.—Four cases were reported after the vaccination campaign started on August 24; these were the last cases of the outbreak.

Comparison with Previous Epidemics

The number of cases compared with those in the previous outbreaks, the months during which they occurred, the case rate, and the fatality rate are shown in Table VI and Fig. 2. It will be noted that there has been a diminished incidence and severity in each successive outbreak. The 1959 outbreak occurred during an unexpected time of the year—that is, the coldest months, as compared with all the previous ones, which occurred during the warmer months. Only the first major epidemic of 1945 had some relationship with a cyclone, as it started soon after a very violent cyclone had caused much damage.

The incidence of cases by district per 100,000 for these outbreaks is shown in Table VII, and the fluctuation within districts over the four outbreaks, standardized on

TABLE VI.—*Incidence and Severity in the Four Outbreaks*

Year	No. of Cases	Period	Case Rate per 100,000	Fatality Rate
1945	1,018	Feb.–April	240	About 6
1948–9	552	Nov.–Feb.	128	5·2
1952	284	March–June	56	1·0
1959	97	June–Sept.	15	Nil

TABLE VII.—*Incidence of Cases by District Per* 100,000

District	1945	1948–9	1952	1959
Port Louis (urban) ..	153·6	119·2	57·9	14·2
Pamplemousses	500·6	187·5	113·1	12·0
Rivière du Rempart ..	355·5	186·0	96·7	17·2
Flacq	185·4	217·9	65·0	15·4
Grand Port	285·6	112·1	79·6	17·1
Savanne	423·5	77·6	70·8	20·6
Plaines Wilhems (urban) ..	210·3	102·9	50·7	16·8
Moka	215·4	90·7	14·8	2·9
Black River	246·1	100·6	42·2	24·2

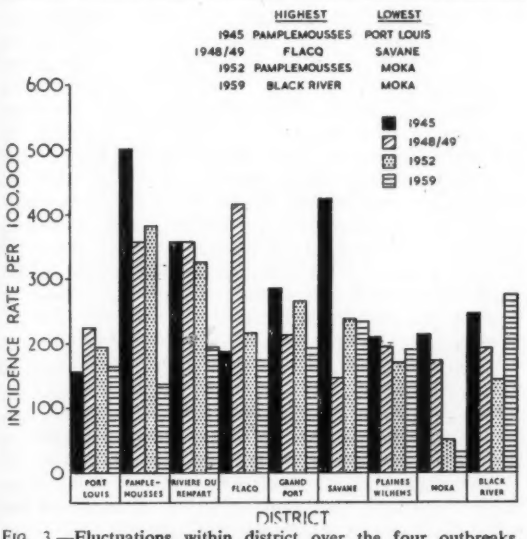

FIG. 3.—Fluctuations within district over the four outbreaks, standardized on that of 1945.

that of 1945, is shown in Fig. 3. In the present outbreak there seems to have been no correlation between the incidence of the disease and the density of population, and the incidence and distribution have been haphazard. However, the north of the island has been more generally affected in the different outbreaks.

In Table VIII the attack rates during the 1945 and 1952 epidemics are compared with those in the 1959 outbreak. These rates have been calculated only where accurate data were available. The tendency for older children to be affected, noticed in 1952 as compared with the 1945 and 1948–9 outbreaks, was not seen in the 1959 outbreak. In this outbreak 87.6% of the patients were under 5 years, and 95.8% under 10 years. The corresponding figures for the other epidemic years are shown in Table IX.

TABLE IX.—*Percentage of Cases by Age-group*

Year	Under 5 Years	Under 10 Years
1945	64·5	95
1948–9	82·2	92·4
1952	77·7	83·4

The estimated population in the various ethnical groups in June, 1959, was: general population, 178,965; Indo-Mauritian, 420,107; Sino-Mauritian, 22,125. The attack rates per 100,000 population in the ethnical groups are shown in Table X, as well as the rates for 1948–9

TABLE X.—*Attack Rate Per* 100,000 *in the Ethnical Groups in Three Successive Outbreaks*

Year	General Population	Indo-Mauritian	Sino-Mauritian
1959	18·9	14·4	18·0
1948–9	72·3*	159·2	
1952	47·5*	77·3	

* Includes Sino-Mauritians.

and 1952. It will be seen that in 1959 the incidence was much the same in the various ethnical groups. In 1945 it was noted that the rate was higher among Sino-Mauritians (who are mostly shopkeepers) than in the other two groups.

As for the duration of the outbreak, the 1948–9 and the 1952 outbreaks, like the present one, also lasted about 14 weeks, with a peak in the 7th–8th weeks.

Influence of Salk Vaccine

The total estimated population on June 30, 1959, in the 1–7 age-group was 125,118. A total of 78 paralytic cases occurred in that age-group.

Among the 25,790 children in that age-group who were not vaccinated there were 72 paralytic cases, while there was only one paralytic case among the 43,395 children who had received three injections of the Salk vaccine. This paralytic case had received three injections in 1957–8. There were four paralytic cases among the 35,603 children who had received two injections of the vaccine: one had received the two injections in September–October, 1957, the second one in September–October, 1958, and the two others in May–June, 1959. In the latter two cases the children fell ill during the third week of July, 47 days and 38 days respectively after the second injection.

In the age group 1–7 years, therefore, the attack rate per 100,000 among those unvaccinated was 279.1 as compared with 2.3 among those who had received three injections. It is thus evident that Canadian Salk vaccine has offered considerable protection against paralytic poliomyelitis.

Influence of Sabin Vaccine

It will be noted (see Fig. 1) that by the time the vaccination campaign with Sabin vaccine had started—---that is, the 11th week—the outbreak had practically come to an end.

Details of the four cases reported after the vaccination campaign started on August 24 are given in Table XI.

TABLE VIII.—*Attack Rate Per* 100,000 *in the Different Ages in* 1945, 1952, *and* 1959

Year	0–4	5–10	0–1	1–	2–	3–	4–	5–	6–	7–	8–	9–	10+
1945	1,070	Not available	400	1,490	1,230	1,230	1,300	1,190	860	340	170	80	Not available
1952	290	23·7	237	388	422	139	36	Not available					13
1959	92	8·8	55	154	115	41	14	15	10	5	11	0	0·94

It will be seen that Case 1 was already ill when the mother took the child to be fed. In Case 2 also there was a suspicion whether the child was really well just before vaccination. The grandfather of the child had died post-operatively in the same house two weeks before the child fell ill, and there was crowding in the house for the funeral. In Cases 3 and 4 careful inquiry did not reveal any history of illness before vaccination. They were the last two cases of the outbreak.

TABLE XI.—*Cases Reported After the Use of Sabin Vaccine*

Case	Age	Date of Onset	Date of Feeding with Sabin	District
1	3 years	21/8/59	24/8/59	Port Louis
2	3 ,,	4/9/59	24/8/59	Pl. Wilhems
3	15 months	6/9/59	24/8/59	Savanne
4	21 ,,	6/9/59	24/8/59	,,

How far the Sabin vaccine has influenced the course of the epidemic may be shown by the laboratory studies on blood and stools now in progress in Johannesburg. These studies will also help in establishing the amount of virus circulating in the community and the state of immunity of the population.

Summary

An outbreak of poliomyelitis due to a type 1 strain occurred in Mauritius during June–September, 1959, and lasted 14 weeks. There were 97 paralytic cases reported, and the attack rate was 15.6 per 100,000 population. There were no deaths.

The maximum incidence was in infancy, 75.5% of patients being under 3 years.

The outbreak occurred "out of season"—that is, in winter.

It started in one district and spread to all districts of the island, and the incidence and distribution within the districts were haphazard.

The incidence in those children aged 1–7 years who had received three injections of Salk vaccine was 2.3 per 100,000 and in those not vaccinated 279.1 per 100,000.

11 weeks after the outbreak started Sabin vaccine type 1 was given to about 195,000 children between the ages of 6 months and 10 years. There were no untoward effects after the vaccination.

I am grateful to Mr. P. Teckham, who was in charge of the orthopaedic centre during the outbreak, and his staff, for allowing me to study the patients, and to Mr. C. A. Bathfield, orthopaedic surgeon, for helpful criticism and advice. My thanks are due to Mr. L. Honoré, director of statistics, and to the Statistical Branch of the Medical and Health Department, for help with the statistical data. I am indebted to Dr. E. Losonczi, Director of Medical Services, for his encouragement and guidance and for permission to publish this report. This paper is intended to serve as a background to a subsequent report which will be published on the outbreak and on the large-scale use of Sabin type 1 vaccine.

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SERUM ENZYME ACTIVITY IN MUSCULAR DYSTROPHY*

BY

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1:6-*Diphosphofructoaldolase* is an intracellular glycolytic enzyme which is particularly abundant in muscle, and its function is specifically the reversible splitting of the molecule of D-fructose-1:6-diphosphate (F.D.P.) into equimolecular amounts of D-glyceraldehyde-3-phosphate (G.-3-P.) and dihydroxyacetone phosphate (D.A.P.). It occurs in serum from normal individuals, where its activity may be altered by disease. The *transaminases* are also intracellular enzymes abundant in muscle; they operate the reversible exchange of α-amino groups, and also appear in the serum. The two transaminases examined here are serum glutamic oxalacetic transaminase (S.G.O.T.), which reversibly catalyses the conversion of aspartic and α-ketoglutaric acids to oxalacetic and glutamic acids, and serum glutamic pyruvic transaminase (S.G.P.T.), which similarly converts alanine and α-ketoglutaric acid to pyruvic and glutamic acids.

Warburg and Christian (1943) and Sibley and Lehninger (1949) reported the incidental finding of hyperaldolasaemia in cases of muscular dystrophy. Sibley later extended the scope of his investigations into the clinical significance of serum aldolase activity to include 880 patients suffering from a wide variety of complaints, among whom were five patients with primary myopathy (Sibley and Fleisher, 1954); he observed that while hyperaldolasaemia occurred in primary myopathy it did not do so in neurogenic muscular atrophy.

Meanwhile Schapira and his co-workers had begun a systematic study of several serum enzymes in progressive muscular dystrophy and related conditions, including aldolase (Schapira, Dreyfus, and Schapira, 1953) and S.G.O.T. and S.G.P.T. (Dreyfus and Schapira, 1955). All three enzymes were found to be elevated in the serum of patients with progressive muscular dystrophy but not in those with muscular atrophy due to disorders of the central or peripheral nervous system. Several workers have since confirmed these original findings (Jacob and Neuhaus, 1954; Beckmann, 1956; Aronson and Volk, 1956, 1957; Pearson, 1957; Evans and Baker, 1957; White and Hess, 1957; Rowland and Ross, 1958; White, 1959; Thompson and Vignos, 1959).

The assay of these serum enzymes has thus become an established procedure in the diagnosis of muscular dystrophy and in the clinical investigation of muscular weakness and atrophy of obscure origin. However,

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although the reports of many workers in this field include a number of undoubted cases of Duchenne type ("pseudohypertrophic") muscular dystrophy, many of the series refer to groups of clinically ill-defined cases of muscular dystrophy from which it is difficult to draw conclusions. The object of the present investigation is to compare the activities of these three enzymes present in the serum of dystrophic patients of different ages, each exhibiting one of four clearly defined clinical forms of the disease, in an attempt to relate these biochemical findings systematically both to the clinical characteristics of the condition and to its duration in the patient. The cases have been classified on clinical and genetic grounds according to the criteria suggested by Walton and Nattrass (1954).

Methods

Serum aldolase may be estimated colorimetrically by the method of Sibley and Lehninger (1949) as carried out by Evans and Baker (1957), or enzymatically by using a coupled system dependent on reduced diphosphopyridine nucleotide (D.P.N.-H) according to the method of Bruns (1954). The unit of activity of serum aldolase determined by either method is reported as μl. of F.D.P. substrate split per hour by 1 ml. of serum under the conditions stated.

In the colorimetric method, serum is incubated with buffered F.D.P. substrate in the presence of hydrazine to trap the G.-3-P. and D.A.P. formed, which are then read against a substrate-free blank similarly treated, after removal of the protein by trichloracetic acid and of phosphate moieties by cold dilute alkali, as the alkaline mixed triose osazones at 540 mμ; initially, determinations of alkali-labile phosphate are made to relate the readings to the amounts of G.-3-P. and D.A.P. formed, so that from them may be derived the aldolase units defined above.

In the enzymatic method* the products of a similar incubation are converted by the addition of triose phosphate isomerase almost entirely to D.A.P., which in turn is then converted to glycerophosphate by D.P.N.-H in the presence of added glycerophosphate dehydrogenase. The rate of formation of D.A.P., and hence the activity of the serum aldolase, is measured by the rate of change of optical density of the system at 340 mμ due to the oxidation of the D.P.N.-H by D.A.P.

S.G.O.T. and S.G.P.T. may each be estimated colorimetrically by the method of Reitman and Frankel (1957), or by the enzymatic method devised by LaDue, Wróblewski, and Karmen (1954) and by Karmen (1955).

In the colorimetric method,† serum is incubated with aspartate/α-ketoglutarate or alanine/α-ketoglutarate substrate respectively, the 2:4-dinitrophenylhydrazone of the reaction product is prepared directly from the treated incubation mixture, and the optical density in excess alkali determined at 505 mμ against water; this is then converted from a standard graph to Frankel units, which are arranged to correspond with those originally defined by Karmen. The results are again expressed as units per ml. of serum.

In the enzymatic method, coupled D.P.N.-H-dependent systems are used as in the estimation of aldolase activity. Oxalacetate and pyruvate produced by the transaminases from their particular substrates are reduced by D.P.N.-H to malate and lactate respectively in the presence of added malic and lactic dehydrogenase, and enzyme activity is determined by the rate of change of optical density of the system at 340 mμ due to the oxidation of the D.P.N.-H.

Results

Estimations of serum aldolase, S.G.O.T. and S.G.P.T. activities have been carried out in a total of 55 patients, of whom 14 were suffering from the Duchenne ("pseudohypertrophic") variety of muscular dystrophy, 15 were cases of the facioscapulohumeral type, 14 were of the limb-girdle type and 12 patients were suffering from dystrophia myotonica. Clinical classification of the cases was carried out independently by two of us (P.L. and J.N.W.), and one of us (W.H.S.T.) was responsible for all biochemical estimations. Of the 14 Duchenne-type cases, 12 were male and all showed typical

TABLE I.—*Serum Enzyme Activities in Patients with Muscular Dystrophy*

Case No.	Age	Sex	Duration of Disease in Years	Degree of Disability	Serum Aldolase (Units)	S.G.O.T. (Units)	S.G.P.T. (Units)
				Duchenne Type			
1	7	M	4	A	55·9	120	134
2	8	M	4	A	119·6	159	135
3	9	M	4	A	105·3	154	185
4	10	M	5	A	111·8	192	154
5	12	M	7	A	43·5	98	110
6	12	M	8	B	38·9	67	66
7	14	M	10	B	39·9	42	23
8	15	M	10	B	22·7	36	27
9	17	M	12	B	18·4	—	—
10	20	M	15	B	15·8	47	32
11	26	M	21	B	13·2	50	35
12	27	M	22	B	13·4	—	—
13	13	F	12	B	10·6	21	19
14	10	F	7	A	30·0	—	—
				Limb-girdle Type			
15	63	M	10	A	5·4	20	15
16	35	M	12	A	5·4	19	11
17	26	M	13	A	14·7	34	18
18	45	M	20	B	5·0	19	11
19	49	M	20	A	4·9	16	13
20	35	M	21	B	5·6	21	16
21	41	F	25	B	1·3	—	—
22	43	F	25	B	6·0	—	—
23	35	F	25	A	4·9	16	13
24	47	M	26	A	5·8	19	13
25	37	M	29	A	8·3	19	12
26	45	M	37	B	8·3	23	15
27	48	M	38	B	7·6	31	38
28	61	F	48	A	3·7	13	8
				Facioscapulohumeral Type			
29	18	M	2	A	22·2	38	23
30	43	M	3	A	11·2	24	16
31	21	M	4	A	11·7	—	—
32	18	M	5	A	7·7	19	13
33	34	F	10	A	7·9	32	26
34	21	F	11	A	10·8	28	17
35	31	F	13	B	9·2	32	17
36	27	F	14	B	7·8	18	14
37	35	F	17	A	4·3	18	17
38	33	F	20	B	7·1	—	—
39	37	F	23	A	3·6	16	9
40	48	M	28	A	8·8	26	22
41	44	F	30	A	4·7	—	—
42	59	F	41	A	4·3	—	—
43	71	F	55	B	3·3	13	4
				Dystrophia Myotonica			
44	18	F	3	A	19·8	36	15
45	22	M	3	A	8·3	20	14
46	25	M	8	B	4·9	22	22
47	30	M	10	A	7·5	37	26
48	34	M	10	B	7·0	16	11
49	35	F	10	B	9·9	26	17
50	38	M	10	A	5·4	21	22
51	37	M	15	B	7·9	19	22
52	60	M	15	A	8·0	26	10
53	48	F	20	A	4·4	27	22
54	35	F	30	A	5·3	19	16
55	58	F	30	A	6·3	28	20

*In this study, both colorimetric and enzymatic methods have been used, and by suitable adjustment of incubation temperatures the same units (Bruns) have been derived from each. Reagents for the enzymatic method were supplied by C. F. Boehringer, of Mannheim (British agents: Courtin and Warner, Ltd., Lewes, Sussex).

†For the colorimetric method of assay, which has been used throughout, standardized reagents were supplied by the Sigma Chemical Co., St. Louis, U.S.A. (British agents: G. T. Gurr, London).

manifestations of this severe form of the disease; two were female and were probably suffering from the more benign autosomal recessive form of Duchenne-type dystrophy (Blyth and Pugh, 1959). All cases of the facioscapulohumeral variety and those of dystrophia myotonica showed the typical pattern of muscular involvement. In the 14 cases of the limb-girdle type, the shoulder-girdle muscles were predominantly or exclusively affected in five, the pelvic girdle in nine. In each category the patients have been arbitrarily divided into two broad groups—namely, A and B—according to the severity of their disability at the time when the estimations were made.

The group A cases were those in whom disability was mild or moderate, and group B those in whom it was severe. Thus most of the patients in group A were still ambulant, while most of those in group B were confined to wheel-chairs or were bedridden. The results of the estimations are given in Table I. These results may be compared with those obtained by Rowell and Smith (1959), who used similar methods of assay, in a series of 50 healthy adults. The normal upper limit (mean + 2S.D.) of serum aldolase activity is taken as 9.2 units (range 2.3–8.8 units, mean 5.7 units), that of S.G.O.T. as 28 units (range 12–36 units, mean 19 units), and that of S.G.P.T. as 21 units (range 4–24 units, mean 12 units). It should be noted that, as Schapira, Dreyfus, Schapira, and Kruh (1955) have pointed out, the mean normal activity of serum aldolase in children aged 5–10 years is approximately twice that of adults. It will readily be seen, however, that age alone could not account for some of the values we obtained in children with muscular dystrophy (Table I). The mean values for serum enzyme activity in the cases of limb-girdle and facioscapulohumeral muscular dystrophy and in dystrophia myotonica are given in Table II. The findings in the Duchenne-type cases are not included in this table, as the values obtained in individual cases

TABLE II.—*Mean Values (in Units) of Serum Enzyme Activity in Certain Types of Muscular Dystrophy*

	Limb-girdle	Facioscapulo-humeral	Dystrophia Myotonica	Normal Adults (Rowell and Smith, 1959)
Aldolase	6·21 (14 cases)	8·31 (15 cases)	7·89 (12 cases)	5·7 (50 cases)
S.G.O.T.	20·8 (12 ,,)	24·0 (11 ,,)	24·8 (12 ,,)	19 (50 ,,)
S.G.P.T.	15·3 (12 ,,)	16·2 (11 ,,)	18·1 (12 ,,)	12 (50 ,,)

varied so widely that the mean of results in this group would possess little significance. However, serum aldolase activity in the male cases of this type is correlated with the age of the patient in Fig. 1, while in Fig. 2 it is correlated with the duration of the disease in cases of all four groups.

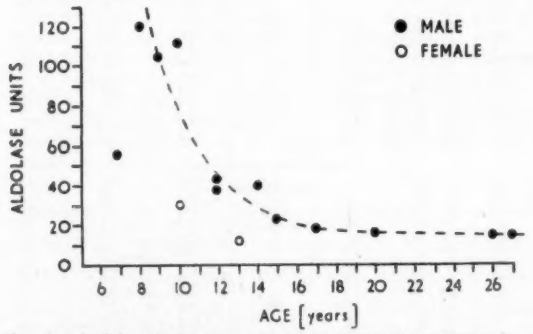

FIG. 1.—Activity of the serum aldolase in cases of the Duchenne-type muscular dystrophy, charted against the age of the patient.

Discussion

The activities of the serum enzymes are remarkably constant for any given healthy individual, a fact which probably indicates a dynamic balance between production and removal. It is often inferred, therefore, that rapid destruction of tissue will temporarily overwhelm the serum clearance mechanisms for those enzymes which are present, and perhaps peculiarly abundant, in that tissue, thus raising their activities in the serum; as, for instance, in the well-known rapid rise of S.G.O.T. activity shortly after myocardial infarction. This simple and attractive hypothesis, however, fails to explain many relevant clinical and experimental findings.

The enzymes isocitric dehydrogenase (I.C.D.) and lactic dehydrogenase (L.D.H.) occur in mammalian heart muscle and liver, the former in considerable abundance; but in myocardial infarction the serum activity of L.D.H. is considerably raised while that of I.C.D. remains normal, and in infective hepatitis the serum activity of I.C.D. is grossly elevated while that of L.D.H. barely exceeds the upper limit of normal (White, 1958). Further, intravenous injection of L.D.H. in dogs raises the serum activity of the enzyme immediately to ten times the normal value, but after one hour the greater part of the L.D.H. has already been cleared from the serum (Wróblewski and LaDue, 1958); and after the intravenous injection of crystalline aldolase in rats the activity of the serum aldolase rises sevenfold within the first 15 minutes, falling almost to normal twelve hours later (Sibley and Lehninger, 1949).

In myocardial infarction it is known that the serum activities of lactic dehydrogenase (Wróblewski, Ruegsegger, and LaDue, 1956) and aldolase (Volk, Losner, Aronson, and Lew, 1956) are raised considerably for several days; yet in view of these high enzyme-clearance rates and the known enzyme content of the myocardium it is difficult to see how the average myocardial infarct could possibly liberate sufficient of these enzymes to maintain a high serum activity for such a period. Similarly, intravenous injection in dogs of purified G.O.T. and G.P.T. concentrates causes a rapid and considerable rise in the serum activities of both enzymes; 24 hours later 97% of the administered G.O.T. has disappeared from the serum and all of it within 72 hours, while in 24 hours only 58% of the administered G.P.T. has been eliminated and after three days 18% of it still remains in the serum (Fleisher and Wakim, 1956). This disparity in serum clearance may perhaps be explained by the molecular weight of G.O.T. being only a third of that of G.P.T. (Green, Leloir, and Nocito, 1945), and in turn may help to explain the later elevation and later return to normal of S.G.P.T. compared with S.G.O.T. activity in cases of moycardial infarction (Rowell and Smith, 1959).

These and other difficulties have led Hauss and Leppelmann (1958) to postulate that the enzyme changes in serum are not due to specific localized tissue damage alone but are part of an "acute syndrome," and represent a complex and non-specific reaction by the entire organism to various afflictions; and they offer certain experimental evidence to support this hypothesis (Hauss, Lepplemann, and Plänitz, 1957). In muscular dystrophy, however, these observations need not apply, since this condition is chronic and in no way an acute syndrome; moreover, it has become evident, particularly in the Duchenne type of muscular

dystrophy, that the enzymes whose serum activities are characteristically elevated in the condition are derived specifically from skeletal muscle.

Normally there is a slight diffusion of aldolase from intact skeletal muscle, which may account for the normal serum activity (Zierler, 1956, 1957); dystrophic muscle, however, shows increased membrane permeability and a much greater efflux of aldolase, and compared with normal muscle it has a greatly reduced total aldolase content (Dreyfus, Schapira, and Schapira, 1954; Zierler, 1958). Furthermore, it has been suggested that the high activity of serum aldolase and S.G.O.T. in malignant cachexia may be due not simply to tumour necrosis but to the nutritional deprivation of skeletal muscle by the protein demands of the tumour, with consequent metabolic distress, wasting, and the liberation of aldolase and G.O.T. into the serum; and it has been found that in the absence of liver metastases the activities in the serum of these enzymes may rapidly be reduced towards normal by massive administration of oral protein and intravenous protein hydrolysate. This treatment, however, entirely fails to influence the raised activities of serum enzymes in muscular dystrophy, thus emphasizing the primary nature of the muscular abnormality (White, 1958).

The primary nature of the lesion is still further emphasized by the fact that in neurogenic muscular atrophy, such as occurs in poliomyelitis, motor-neurone disease, nerve injury, and polyneuritis, normal serum activities of aldolase (Schapira, Dreyfus, and Schapira, 1953; Aronson and Volk, 1957; Thompson and Vignos, 1959) and G.O.T. (Siekert and Fleisher, 1956; Pearson, 1957) occur even when the rate of muscular wasting, as in convalescent poliomyelitis, is proceeding at a rate much greater than is seen in muscular dystrophy. In the acute phase of neurogenic muscular atrophy of sudden onset there may be an initial trivial rise in the serum activities of these enzymes, but this is always transient and very quickly reverts to normal; experimental confirmation of these observations has been forthcoming for both aldolase and G.O.T. by carrying out surgical nerve section in dogs (Aronson and Volk, 1957).

The validity of any observation on the serum enzyme activity in muscular dystrophy depends first on accurate clinical diagnosis of the type of dystrophy from which the patient suffers. In several recent publications the accuracy of clinical diagnosis and classification was open to doubt. In this study diagnosis and classification were carried out according to rigid

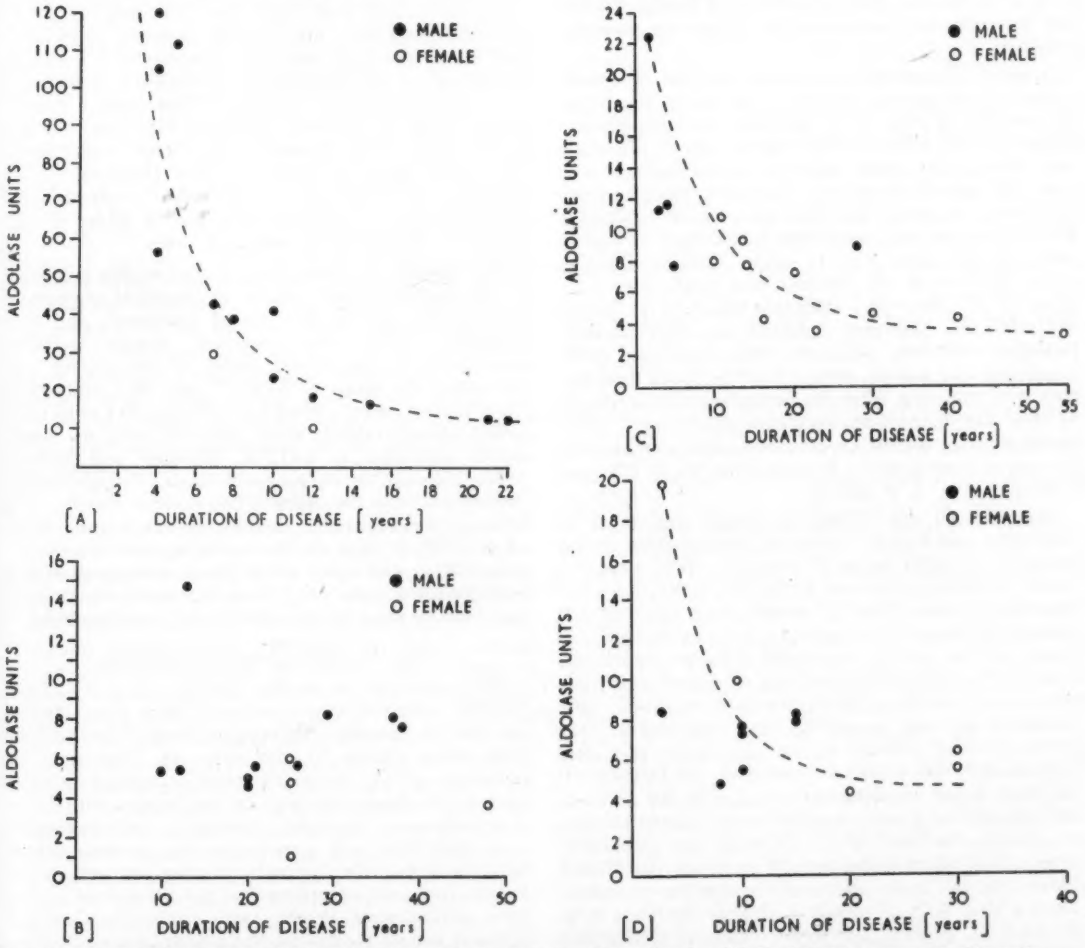

FIG. 2.—Activity of the serum aldolase charted against the duration of the disease. (A) Duchenne-type muscular dystrophy. (B) Limb-girdle muscular dystrophy. (C) Facioscapuloh umeral muscular dystrophy. (D) Dystrophia myotonica.

clinical and genetic criteria, and in most cases the diagnosis was confirmed by electromyography and often by muscle biopsy. We have determined in serum the activities of the three enzymes—aldolase, G.O.T., and G.P.T.—in four clearly defined clinical forms of the disease—namely, in 14 cases of Duchenne-type dystrophy, 14 cases of limb-girdle dystrophy, 15 cases of facioscapulohumeral dystrophy, and in 12 cases of dystrophia myotonica.

Duchenne Type of Muscular Dystrophy

In our series of cases of the Duchenne type of muscular dystrophy the patients ranged from active 7- and 8-year-old boys to immobile and helpless terminal cases in 26- and 27-year-old men. In the early stages of the disease very high serum activities of aldolase were found, falling steadily as the disease progressed, until in terminal cases the activity was not greatly raised above the upper limits of normal. Plotting age against these serum aldolase activities gave characteristic graphs (Fig. 1), starting with very high and rather scattered readings in the young active cases, falling steeply with increase in age, and latterly falling much less steeply among the advanced cases, where there was no significant scatter. There are indications (Thompson and Vignos, 1959) that wide individual variation tends to occur in the serum aldolase activities of young patients, and that this may sometimes be related to muscular activity.

Graphical representation against duration of disease instead of age gave a similar graph which was rather less convincing (Fig. 2, A) probably because, given a disease process which usually begins early in life and a rate of evolution which tends to remain constant with time, the age of the patient provides a more accurate indication of status than does duration of symptoms. The two female patients in this series, aged 10 and 13 years, showed (see Fig. 1) serum aldolase activities which were much less elevated than might have been expected for their age, a finding which is in accord with the sex difference reported by other workers (Schapira, Démos, Schapira, and Dreyfus, 1957; Thompson and Vignos, 1959). Very probably these two girls were suffering from the benign autosomal variety of the Duchenne-type muscular dystrophy. Their serum aldolase activities were comparable to those seen in cases of limb-girdle or facioscapulohumeral muscular dystrophy (Fig. 2, B and C).

Our findings are in full agreement with those of Thompson and Vignos (1959), who have derived similar graphs in a larger series of patients. They adduce a linear relationship between serum aldolase activity and functional muscle mass by means of an involved and exhaustive physical examination of muscle bulk and power in each patient, showing that the serum aldolase activity diminishes with the mass of muscle still functional and therefore, given constant evolution, with increasing age and decreasing functional ability. The graph of serum aldolase activity against age of patient may possibly be explained, therefore, as follows. It has been shown experimentally that, after the intravenous injection of known amounts of crystalline aldolase in animals the rate of clearance of the aldolase is proportional to its initial activity in the serum (Sibley, 1958). In the early stages of the disease, therefore, when a large bulk of muscle is steadily liberating large amounts of aldolase, the serum-clearance mechanisms are probably saturated and high serum activities of aldolase result; later, when the muscle bulk has diminished and with it the amount of aldolase entering the serum, the accelerated clearance mechanisms may be better able to meet the demands now made and the activity of serum aldolase falls rapidly. Finally, when there is little muscle left and a minimal liberation of aldolase, the stimulus of serum activity towards clearance of aldolase falls steadily away as does the remaining muscle bulk, and thereafter the passage of time has little effect on the serum aldolase activity, which remains now only slightly raised above the upper limit of normal.

Recent investigations indicate that in dystrophic patients the increased transaminase (G.O.T.) activity of the serum is derived, like that of aldolase, from the diseased skeletal musculature, but that the ratio of its activity to that of aldolase in healthy skeletal muscle is only a sixth of that in the myocardium (White and Hess, 1957); further, homogenates of healthy cardiac and skeletal muscle both display G.O.T. activity about 20 times greater than that of G.P.T., the activity of each of these enzymes being about one and a half times greater in cardiac muscle than the corresponding activities in skeletal muscle (Wróblewski and LaDue, 1956). In our series of 10 male cases of representative ages with Duchenne-type muscular dystrophy, however, we have found that both S.G.O.T. and S.G.P.T. activities were very high in the youngest cases, and that these activities decreased progressively with the increasing age and disability of the patient and thus with the corresponding diminution of functioning muscle mass. Even in terminal cases they still exceeded the upper limits of the normal range. Our results agree fully with those of other workers (Pearson, 1957; Murphy and Cherniak, 1958), who confined their investigations to S.G.O.T. only, but in larger though not more representative series of cases.

The findings, however, were not so readily amenable as the serum aldolase activity to graphical representation against age or duration of symptoms, and thus provided rather less sensitive, though reliable, indications of the clinical status of the patient. In our series the mean of S.G.O.T. was 96.5 units (5.08 times normal mean) and of S.G.P.T. was 90.1 units (7.51 times normal mean), which accords with the much slower clearance of S.G.P.T. (Fleisher and Wakim, 1956) outweighing its probably lesser, though steady, production from the degenerating skeletal muscle. The ratio of the dystrophic multiple of the normal mean of S.G.P.T. to that of the normal mean of S.G.O.T. was 1.48 in our series of 10 cases, compared with a corresponding ratio of 1.59 in the series of 30 cases reported by Dreyfus, Schapira, and Schapira (1958).

Other Varieties of Muscular Dystrophy

The activities of serum aldolase, S.G.O.T., and S.G.P.T. obtained in our cases of three other clinical varieties of muscular dystrophy were much less striking than those shown by the cases of Duchenne-type dystrophy, though the mean values exceeded normal in each of the three varieties. In the patients with facioscapulohumeral muscular dystrophy and dystrophia myotonica there was a moderate rise in mean values, while in limb-girdle dystrophy the rise was only slight. It is at first sight surprising that the mean level should have been higher in the very benign facioscapulohumeral variety than in the less benign limb-girdle type. This can be explained by the fact that the series of

facioscapulohumeral cases was "weighted" by the inclusion of four early cases, while in no patient in the limb-girdle group had the disease been in progress for less than 10 years. In none of the three forms, however, was there such gross elevation of the serum enzyme activities as in the Duchenne type of dystrophy with its very rapid and extensive evolution and grave prognosis. In only 5 out of 15 cases of the facioscapulohumeral type, 2 out of 12 cases of dystrophia myotonica, and 1 out of 14 cases of the limb-girdle type was there a significant, though moderate, increase of serum enzyme activity, particularly of aldolase. This always tended to occur in younger cases of shorter duration with a greater functioning muscle mass. Similar sporadic and modest elevations of serum enzyme activity in these clinical forms of muscular dystrophy have been reported in the smaller series studied by other investigators (Pearson, 1957; Rowland and Ross, 1958; Kuhn and Wörner, 1959; Salvi, Ambanelli, Rosati, Carreras, and Mironi, 1959; Thompson and Vignos, 1959).

Conclusions

It is concluded that assay of these serum enzyme activities, particularly of aldolase, is of considerable value in the diagnosis of muscular weakness of insidious onset and obscure origin in young children, particularly in boys. Normal findings do not exclude a neurogenic origin but do exclude a diagnosis of Duchenne-type dystrophy, while greatly increased levels in the absence of other florid disease confirm its presence and carry a correspondingly grave prognosis. In older children and in young adults the same observations apply; though the diagnosis of the Duchenne-type dystrophy will usually be evident clinically at this stage, it will be supported by the finding of greatly raised serum enzyme activities. In the other and milder clinical forms of muscular dystrophy discussed here the serum enzyme activities afford little help since normal findings do not exclude the diagnosis. It must also be admitted, in agreement with the views of other workers, that the findings of increased activities of these enzymes in the serum appears to be a secondary result of leakage from diseased muscle cells. There is no evidence that any disorder of function of any of the enzymes referred to is of fundamental importance in the pathogenesis of the disease.

Summary

The serum activities of the enzymes aldolase, glutamic oxalacetic transaminase, and glutamic pyruvic transaminase, have been estimated in 55 cases of muscular dystrophy (14 Duchenne type, 14 limb-girdle, 15 facioscapulohumeral, 12 dystrophia myotonica).

In the Duchenne-type dystrophy the serum activity of all three enzymes was elevated at every stage of evolution of the disease, being particularly high in the early stages and lower terminally. A quantitative relationship, which appears to depend upon the amount of functioning muscle mass, was demonstrated to exist between the serum aldolase activity and the age of the patient. In the other varieties of muscular dystrophy only moderate and sporadic increases in the serum activities of these enzymes were discovered, but again the highest activities were always obtained in the early stages of the disease. Even in these comparatively benign varieties of muscular dystrophy, however, the mean serum activity of the three enzymes was raised above normal.

It is concluded that estimation of the serum aldolase activity is of considerable value in the diagnosis of the Duchenne-type muscular dystrophy, but it is of little help in the diagnosis of the other varieties. These abnormalities in serum enzyme activities probably indicate pathological diffusion of enzymes from diseased muscle cells, but evidence is still lacking that disorder of their function is fundamental in the pathogenesis of progressive muscular dystrophy.

We are grateful to Dr. A. L. Latner for providing facilities for these investigations in the department of chemical pathology of the Royal Victoria Infirmary, and also to Dr. A. J. Smith for assistance with transaminase estimations; one of us (W. H. S. T.) wishes to thank Dr. E. B. Hendry and Dr. John B. Gaylor, of Glasgow Western Infirmary, for their encouragement in the continuation of these investigations. The diagrams were prepared by Miss M. Mustart in the department of photography, King's College.

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Rumania has undertaken a nation-wide five-year plan of cancer control and is spending $23m. to develop hospital services, dispensaries, and training facilities.

MALIGNANT EFFUSIONS TREATED BY COLLOIDAL RADIOACTIVE YTTRIUM SILICATE*

BY

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Intracavitary isotope therapy of malignant effusions in peritoneal and pleural cavities is now commonly practised in many departments. The most frequently used isotope is colloidal radioactive gold (^{198}Au), and details may be found in standard texts of isotope therapy—for example, Hahn (1956) and Beierwaltes *et al.* (1957). Our own experience has also been described (Walter, 1953). It is a form of internal "bath" therapy, in which the serous linings are subjected to irradiation by beta-particles of low penetration (Table I). The mode of action, as well as the mechanism of production of the effusions, is only imperfectly understood. Some of the possible factors include a direct damaging effect on superficial cancer cells, obliteration of capillary blood-vessels and lymph vessels, formation of fibrous layers on the surfaces, and irradiation of local lymph nodes by transported material. The method, however, is clinically effective, and has been found to give useful palliation in about one-third to one-half of the cases treated. The most favourable subjects are those in reasonably good condition, where the repeated effusion is the chief cause of symptoms and there are no large masses of growth. Since the technique is simple and involves only slight inconvenience to the patient, this treatment marks a definite advance in the handling of malignant exudates, as they are usually uncontrollable by present-day conventional external radiation.

In addition to the betas, however, ^{198}Au gives off a fraction of penetrating gamma-radiation†. This has the advantage of making it easy to detect and plot the distribution of active material by a Geiger-counter outside the body. Otherwise it is generally regarded as undesirable, as it gives an unwanted total-body fraction of radiation to the patient, increases the radiation background in the ward (exposure of nurses, etc.), and materially complicates the problem of handling and dispensing, with hazards to physicists, doctors, and others. Search was therefore made for pure beta-emitting isotopes with appropriate characteristics, and interest has centred mainly on two such: (1) phosphorus-32 in the form of colloidal chromic phosphate, and (2) yttrium-90 in various preparations, including the ionic chloride, colloidal phosphate, fluoride, hydroxide, and now the silicate ($^{90}Y_2(SiO_3)_3$).

Chromic phosphate has been tried (Root *et al.*, 1954), but does not seem to have established itself, possibly owing to the relative difficulty of preparing it.

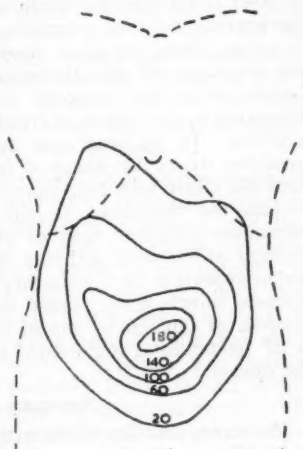
Physical Properties of Yttrium-90.—There are two methods of preparation—(1) from decay of strontium-90, which is a fission product of the breakdown of uranium in the nuclear reactor; and the ^{90}Y thus obtained by separation is *carrier-free*—that is, unmixed with atoms of stable non-radioactive yttrium (^{89}Y); (2) from irradiation of stable ^{89}Y in the nuclear reactor; variable amounts of carrier yttrium will be present, depending on the specific activity obtainable (which in turn depends on the neutron flux available in the reactor). ^{90}Y is prepared at present at Harwell by the second method, and this was used to produce the silicate colloid (Cook *et al.*, 1958). Table I lists the chief physical properties of interest to the therapist. The beta is much more energetic than that of ^{32}P or ^{198}Au and consequently penetrates to a greater effective distance below the surface. The old argument against the use of pure beta-emitters—that is, that they could not be detected by counters external to the body—is no longer valid, since modern *scintillation counters* can use the "bremsstrahlung"‡ from ^{90}Y betas to give isodose plots quite comparable to those from ^{198}Au (see Fig.).

TABLE I.—*Physical Properties of ^{198}Au, ^{32}P, and ^{90}Y*

Isotope	Half-life (Days)	Maximum Beta Energy (MeV)	Mean Beta Energy (MeV)	Maximum Range in Tissue (mm.)	Half-value Thickness* (mm.)
^{198}Au	2·7	0·960	0·32	3·8	0·245
^{32}P	14·3	1·707	0·70	7·6	0·65
^{90}Y	2·7	2·260	0·90	10·5	0·98

* Depth in tissue at which dose has fallen to half that at surface.

Biological Properties of Yttrium-90.—The rare-earth elements, of which yttrium is a member, have been subjected to recent intensive study—biochemical, pharmacological, and metabolic (Kyker and Anderson, 1956). There is very little absorption of *ionic yttrium* after oral, subcutaneous, or intramuscular administration; any fraction reaching the blood-stream is deposited mainly in the skeleton, as yttrium is a *bone-seeker*; much smaller amounts are excreted or taken up by liver and spleen. After intravenous injection the highest uptake is in liver, spleen, and bone-marrow; in fact, ionic yttrium behaves like a colloid, and forms complexes with body proteins. After intracavitary injection, the amount retained in the cavity depends largely on the amount of carrier; with high carrier content, over 90% may be retained and deposited more or less on the serous surfaces (Lewin *et al.*, 1954; Andrews *et al.*, 1956).



Isodose contours obtained from the "bremsstrahlung" after intraperitoneal injection of radioyttrium silicate.

*Based on a paper presented at the International Congress of Radiology, Munich, 1959.

†For the relative dose due to gamma-radiation a figure of 10% is sometimes given; however, the ratio will vary considerably with the physicial conditions and the point of interest.

‡From the German "Bremse"=brake, and "Strahlung"=radiation. The impact of the betas on the atoms in tissue gives rise to *x* rays, some of which are sufficiently penetrating to emerge from the body and affect an external counter. These rays are exactly analogous to ordinary *x* rays produced by the impact of electrons (beta-particles or rays) in an *x*-ray tube when they are suddenly halted by the target.

Ionic yttrium has been found to be toxic—for example, to mice (Cook *et al.*, 1958), but if we can extrapolate their findings on a weight basis to man there seems to be no real danger; the chloride has been used with apparent success at high carrier levels in patients (Siegel *et al.*, 1956).

Present Investigation

Our work was preceded by an investigation at Harwell using mice (Cook *et al.*, 1958), where a comparison between yttrium chloride, colloidal yttrium silicate, and colloidal gold showed a preferable overall distribution in favour of the silicate.

Preliminary investigation on patients was begun with tracer quantities of the silicate (about 200 μc.) injected into malignant effusions. The levels of activity in blood in the first few days were found to be low—for example, 0.002–0.02% of administered dose per litre—with correspondingly low urinary output—for example, less than 1% integrated over five days. One post-mortem tissue assay became available six days after 240 μc. intraperitoneally; this showed low values—for example, the centre of the liver contained 0.00128% per g., which corresponded to 178 rads for a therapeutic injection. A comparable figure (for liver dosage) obtained after 200 mc. of ^{198}Au was 380 rads (Walter, 1953).

Since the tracer investigation pointed to the safety of the new compound, a therapeutic series was begun of patients with intractable effusions. Some of them were in poor condition, with a very bad prognosis because of the extent of growth. It is not very surprising, therefore, that out of 15 patients treated 6 died within one month. These have been neglected in the following assessment, as giving no useful indication of the value of the method.

The quantities injected ranged from 21 to 75 mc., according to the amounts available from Harwell, which were limited. The specific activity obtainable was low, so that the fluid volumes to be instilled ranged from about 100 to 400 ml.; this was of no great moment in abdominal cases, but sometimes involved larger volumes in the chest than we would have wished. The technique was simple, and identical with that used for gold (Walter, 1953). After previous tapping of most of the exudate, a simple funnel with tubing was used to instil the first 50 ml. of saline, then the colloid, then a final 50–100 ml. of saline to flush the tubing, all by gravity feed. The patient was rotated in the theatre and later in the ward, and intermittent raising of the foot of the bed for several hours all helped to ensure good mixing and as uniform a distribution of the isotope as conditions allowed. Samples of blood and cavity fluid were withdrawn at intervals, so far as the patient's condition permitted; urine was estimated in daily batches; and a body scan was made after 24 hours. Distribution was almost always satisfactory; one case of loculation was found. General reactions were minimal, and there was no obvious effect on the blood count.

TABLE II.—*Results of Treatment with Intracavitary Radio-yttrium Silicate.* (*Total Cases*, 15. *Died Within One Month*, 6)

Pleural	Peritoneal
Satisfactory at 5 months	Satisfactory at 5 months
,, ,, 5 ,,	,, ,, 10 ,,
,, ,, 9 ,,	No effect at 6 months (died)
,, ,, 19 ,,	,, ,, ,, 14 ,,
No effect at 8 months (died)	

In all pleural cases the primary was in the breast. In all peritoneal cases the primary was in an ovary.

Table II summarizes the clinical results. "Satisfactory" connotes reasonable freedom from symptoms and the need for tapping. Out of the nine cases listed, therefore, useful palliation was achieved in six, for periods of time ranging from 5 to 19 months. The number is, of course, small, but these results compare very favourably with those reported for ^{198}Au by ourselves and others, in the region of 50% receiving useful palliation.

Blood and urine levels never gave cause for anxiety—for example, 0.001%/litre in blood at four hours and 0.003% at 29 hours; and 0.04% in urine integrated over 48 hours. Three post-mortem assays were made at 11, 3, and 1.5 days after injection; the liver doses corresponded to 244, 4.7, and 12 rads respectively.

Serial assays of cavitary fluid showed that in most cases (9 out of 12) precipitation was quite marked and quite rapid, as judged by the concentration of activity in the fluid—for example, 7.4%/litre at four hours and 3.3% at 48 hours. After the first day the fall of activity in the fluid was only gradual.

Discussion

From the physical standpoint the most striking feature of ^{90}Y in the present context is its energetic beta-radiation (Table I) and consequent superior depth-dose as compared with gold or phosphorus. In order to compare depth-doses, we must make some assumptions about the geometrical conditions in the body cavities, concerning the possible thicknesses of fluid layers, etc. It can then be shown that the ratio of depth-dosage ^{90}Y/^{198}Au rises to a maximum of about 3.1–3.6 at a depth of 1.5 mm. The effective ratio for ^{90}Y/^{198}Au will, of course, vary with the physical conditions obtaining, but a tentative figure might be between 2 and 3.

Yttrium compounds have not yet received extensive clinical investigation as intracavitary agents. Most of the work published so far concerns preliminary animal, or human tracer, investigations. Of this work, most has been done with yttrium chloride, and it gradually became clear that large carrier quantities of yttrium were necessary to ensure adequate localization in the cavity. One therapeutic series has been reported from New York (Siegel *et al.*, 1956); 10–30 mc. of ^{90}Y as chloride was used, with 100–200 mg. of yttrium carrier, and 8 out of 16 patients derived useful benefit. The levels in blood, urine, liver, etc., reported by them appear to be roughly comparable with ours.

Theoretically, early precipitation on to the serous surfaces would seem desirable in order to achieve the maximal radiation effect. High-carrier chloride seems to deposit more slowly than the silicate, if we compare our findings above with published reports (Laszlo, 1956; Andrews *et al.*, 1956). This is a possible advantage of the silicate, if our findings are typical. The actual distribution on the serous surfaces is very irregular indeed, as our post-mortem assays showed, but this is not likely to be due to inadequate mixing, which would be expected to show up in the body scan (see Fig.) Similar wide variations are also found with ^{198}Au (Walter, 1953).

From the standpoint of protection and diminution of radiation hazard to personnel, there is no question that ^{90}Y would be a boon as compared with ^{198}Au. If experience confirms its safety, it could well replace ^{198}Au for intracavitary work. Nowadays, of course, intracavitary isotope therapy has to compete with chemotherapy

(intracavitary nitrogen mustard, thiotepa, etc.), but it still has a place where alternative methods fail, as they often do.

The comparative merits and demerits of the various preparations of yttrium have still to be determined and checked against clinical experience. In the colloidal silicate we appear to have a substance of promise, worthy of further investigation.

It is proposed to publish elsewhere full technical details of the above investigation, including physical data on dosage, post-mortem assays, activity in blood, urine, and cavitary fluid, etc.

Summary

As an alternative to radioactive gold for control of malignant pleural and peritoneal effusions, the use is described of a new compound, colloidal radioactive yttrium silicate ($^{90}Y_2(SiO_3)_3$). A preliminary report is made of its therapeutic use in 15 cases. Out of nine cases surviving over one month, six received good palliation for 5 to 19 months. The advantages of yttrium over gold are discussed, especially the superior surface penetration of the beta-particles and the lesser radiation hazards owing to absence of penetrating gamma-radiation.

Thanks are due to my physicist colleagues, on whom this work depended, in particular Mr. J. C. Jones (now at the Royal Marsden Hospital, London), and Mrs. Monica Fisher; to my colleague, Dr. Frank Neal, for helpful liaison; to Mrs. Ruth Martin for secretarial assistance; and to Miss D. Wemm for the Figure.

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"The aims of the Association of Social Workers and also present-day thought in social work show that there are elements common to all social work practice whatever its setting. To discern these common elements, recast them as a discipline and find effective ways of teaching them is a major challenge which merits special study and research. Evaluation studies of techniques in casework are needed and the criteria of success and failure in casework practice require to be explored. So far only small sporadic studies of this kind have been made in Britain. The probation field with its preponderance of unwilling clients would seem to offer a unique opportunity for comparative studies into the histories of such clients and for analysing the ways in which they can be enabled to draw help from the relationship with the worker and from the resources of the community. Such studies might well have a bearing on future social planning and could usefully have a wider reference to include analyses of existing training, work studies, and job evaluations in each of the social work specialties." (*Evidence Submitted to the Departmental Committee on the Probation Service*, Association of Social Workers; price 1s. 6d.)

DYSTROPHIA MYOTONICA IN CHILDHOOD

BY

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The clinical development of dystrophia myotonica in adults is commonly the following: a family history of senile cataracts in an early generation, of presenile cataracts in the next, and finally the full picture of the disease in the third. The early development and evolution of the disease in infants and children, of whose parents one may show only certain features of dystrophia myotonica, is less familiar. Six such cases have been seen at the Hospital for Sick Children in the past five years. Only three cases of myotonia congenita are recorded over the same period, and yet this disease, while it, too, is rare, is reputedly of earlier onset than dystrophia myotonica. Though the two diseases present differently and have a widely different prognosis, there is no doubt that they are interrelated. There are records of patients with myotonia congenita diagnosed in childhood who many years later developed stigmata of dystrophia myotonica; also of families in which the two diseases have occurred in different individuals (Maas and Paterson, 1950; Walton and Nattrass, 1954).

Because dystrophia myotonica is not widely recognized as a cause either of flaccid paresis in infancy (amyotonia congenita syndrome of Oppenheim) or of congenital facial diplegia the following cases are reported.

Case Histories

The diagnosis was made while the child was under the care of the physician whose name appears in parentheses, and at the first age mentioned. When a second figure for age is given this indicates the length of follow-up. In no family is there parental consanguinity.

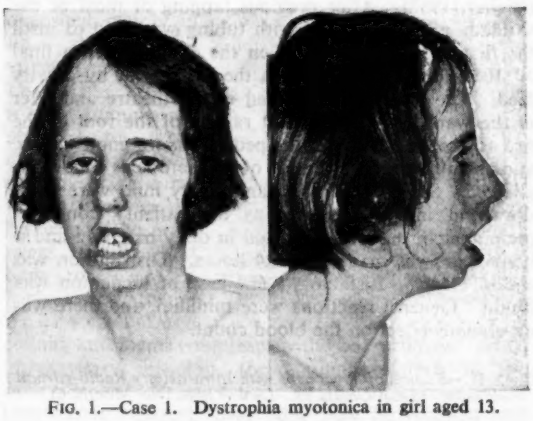

FIG. 1.—Case 1. Dystrophia myotonica in girl aged 13.

Case 1.—Girl (Dr. P. H. Sandifer) 13 years (Fig. 1). Breech delivery after normal pregnancy. Bilateral talipes noted shortly after birth. Difficulty with sucking. Floppy infant. Delayed motor and speech development. Assessed as ineducable. No history of deterioration in performance. On examination: mentally retarded. Complete bilateral facial paralysis, ptosis, wasted temporal muscles but strong

masseters, nasal speech, poor palate movement, string-like sternomastoids. Receding hairline. Myotonic grip and percussion reaction of thenar, pectoral, and deltoid muscles. Generalized feeble muscle power, especially in pelvic girdle, peronei, and tibialis anterior. Kyphoscoliosis. All tendon reflexes present and brisk except ankle jerks. Below third percentile in weight. Skull *x*-ray examination: small pituitary fossa, large frontal sinuses. Her mother, who denies any disability, has ptosis, myotonic grasp, and percussion reaction of thenar muscles. The eldest sibling, aged 20, is normal, but two older brothers are mentally retarded and have foot deformities. They have not been examined.

Case 2.—Boy (Dr. P. H. Sandifer) 11 to 13 years. Normal pregnancy and delivery. Difficulty with sucking. Floppy infant. Delayed motor and speech development; walked alone at 2 years. Attends school for educationally subnormal children. Recent history of deterioration in gait from progressive weakness of peroneal and anterior tibial muscles. Examination disclosed complete bilateral facial paralysis, weak masseters, wasted temporal muscles, string-like sternomastoid on right, absent on left. Myotonic grasp and thenar percussion reaction. Generalized muscle feebleness, most pronounced in upper arm, peroneal, and anterior tibial muscles. Foot-drop gait. All tendon reflexes brisk except absent left ankle-jerk. Dorsal scoliosis. Normal testicles. Weight at 13 years below third percentile. Skull *x*-ray examination: thickened calvarium and small pituitary fossa. Only sibling (Case 3) had dystrophia myotonica. Mother (who died from the effects of rheumatic heart disease) had ptosis, sternomastoid wasting, myotonic grip, and thenar percussion reaction without being aware of these abnormalities.

Case 3.—Girl (Dr. P. H. Sandifer) 4 to 8 years. Normal pregnancy, breech delivery. Bilateral talipes noted at birth. Normal sucking. Floppy infant. Retarded motor and speech development. Attends school for physically handicapped. No subjective or objective deterioration. Examination showed marked facial weakness, most obvious in the forehead, ptosis, wasted temporal muscles, string-like sternomastoids, nasal speech, poor palate movement. Receding hairline. Myotonic grasp and thenar percussion reaction. Generalized muscle feebleness, most marked peripherally. All tendon reflexes brisk except ankle-jerks. Fixed talipes equinovarus deformity. At 8 years below third percentile in weight and tenth in height. Skull *x*-ray examination: small pituitary fossa. Serum aldolase, wrist bone age, and E.C.G. normal. I.Q. 60 (all at the age of 8).

Case 4.—Boy (Dr. R. Lightwood) 6 to 10 years. Normal pregnancy and delivery. Normal sucking. A floppy infant, but was sitting at 9 months and walking at 15 months. Late speech development. Attends school for physically handicapped. No subjective or objective deterioration. On examination, facial weakness most pronounced in forehead, wasted temporal and sternomastoid muscles, nasal speech, and poor palate movement. Myotonic grip and percussion reaction of thenar muscles. Generalized feeble muscles, especially peripherally. Tendon reflexes absent in upper but brisk in lower limbs. Normal testicles. Weight between third and tenth percentiles at 6 and 10 years. Electromyogram (Dr. A. T. Richardson): right wrist flexors; evidence of myotonia. Skull *x*-ray film: normal (6 years); thickened vault, normal pituitary fossa (10 years). Bone age (10 years) normal. E.C.G. normal (6 and 9 years). I.Q. (6 years 6 months), 80–90 on revised Stanford Binet scale, 70 on Merrill Palmer scale. At 6 years 11 months, 85 on revised Stanford Binet scale. At 8 years 7 months, 78 on revised Stanford Binet scale. At 9 years 2 months, 73 on revised Stanford Binet scale. At 10 years 5 months, 70 on revised Stanford Binet scale. One normal sister aged 4. Mother severely affected, including cataracts.

Case 5.—Boy (Dr. P. R. Evans) 14 months to 3 years 10 months. Normal pregnancy but feeble intrauterine movements. Breech delivery. Difficulty with sucking. Bilateral talipes noted at birth. Floppy infant. Retarded motor and speech development. Continues to gain skills. On examination, bilateral facial paralysis, wasted temporal muscles, weak sternomastoids. Floppy infant with generalized muscle feebleness especially in peroneal and tibialis anterior muscles. No myotonic phenomena noted until 3 years old, when relaxation of calf muscles was noted to be slow. Leg tendon reflexes and supinator jerks brisk, biceps and triceps reflexes absent. Left testicle normal, right undescended. Normal height and weight throughout. Electromyogram (Dr. E. D. C. Campbell) normal. Serum aldolase and skull *x*-ray film normal. Urine creatine coefficient, 11.4 (raised). Urine creatinine coefficient, 13.2 (normal). Muscle biopsy of tibialis anterior, using Cöers and modified Koelle techniques (Dr. M. Bodian): sacrolemmal nuclei increased in number, and rows of these lined up on the periphery but not in the centre of muscle fibres. Nerve-endings normal. (All at 14 months.) Mother has minimal signs of dystrophia myotonica, but her brother is severely affected. Of two children of the mother's previous marriage, one is retarded in motor development and is said to have a myotonic grip.

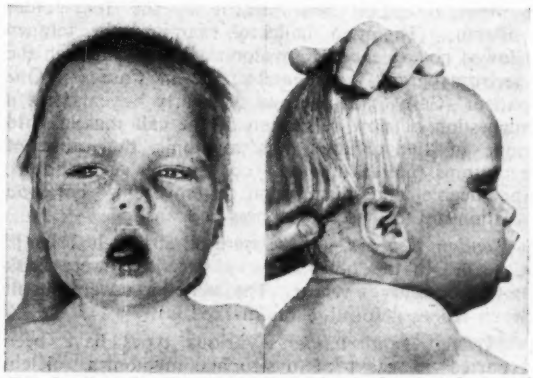

FIG. 2.—Case 6. Dystrophia myotonica in female infant aged 9 months.

Case 6.—Girl (Dr. P. R. Evans) 9 months (Fig. 2). Normal pregnancy and delivery. Difficulty with sucking. Floppy infant. Not lifting head or sitting up. On examination, poor facial movements, wasted temporal muscles, weak sternomastoids, poor tongue movements, high arched palate. Floppy infant; all reflexes present. No clinical evidence of myotonia. Electromyogram (Dr. E. D. C. Campbell): tibialis anterior and extensors of forearm; typical myotonic pattern with minimal dystrophic (myopathic) signs. Serum aldolase, 20.2 μmol. per 100 ml. per hour (slightly raised). Urine creatine coefficient, 9.5 (raised). Urine creatinine coefficient, 6.1 (low). Mother has myotonic grip, of which she is aware but which is not a cause of severe disability. Her temporal muscles are wasted. Her brother is severely affected and has cataracts. The maternal grandfather's sister had cataracts. The patient has an older normal male sibling.

Clinical Features of Dystrophia Myotonica in Childhood

Muscle-wasting.—As in adults, wasting of the temporal, facial, and sternomastoid muscles is an early and characteristic feature. All these children had obvious wasting of the temporal muscles. Four had facial paralysis at birth, causing difficulty with sucking. Two (Cases 3 and 4) had no such difficulty, but when first seen, at 4 and 6 years respectively, there was obvious lack of facial expression with paresis, most pronounced in the upper half of the face. The string-like sternomastoids complete the characteristic appearance: a long, swan-like neck, a long face tapering towards the jaw, with hollow temporal fossae. Ptosis

was noted in Cases 1 and 3. In three children palate movement was poor and resulted in nasal speech, as in some adult cases. In no case was myotonia or wasting obvious in the tongue, though one patient (Case 6), at 9 months, is noted to have poor movements of the tongue. The other muscles selected for atrophy have shown a variability at least as great as that reported in adults (Maas, 1937). In Case 1, for instance, the greatest weakness was in the pelvic girdle, whereas in Case 2 the distal leg muscles were most severely affected. All these children were limp and floppy infants (see below). It is noteworthy that three children were found to have bilateral talipes at birth. In only one (Case 5) has early correction given good results. He has, however, marked weakness of the peroneal and tibialis anterior muscles. Ford (1952) mentions the case of a woman whose history went back to infancy, during which she was noted to have an immobile face and club-feet.

Myotonia.—This was present in the four older children. The two children examined in infancy showed no evidence of myotonia clinically, though the electromyogram was characteristic in Case 6. One patient (Case 5) at the age of nearly 4 years has a suggestion of slow relaxation of the calf muscles. In none of the children was myotonia the cause of symptoms (unlike myotonia congenita). As in adults, the degree and distribution of myotonia bore no relationship to muscle weakness and wasting.

Tendon Reflexes.—These were all strikingly brisk in Case 6. In the other children knee-jerks were brisk but other reflexes varied. The ankle-jerks were absent when talipes deformity was marked.

Skeletal Abnormalities.—Various types have been reported in cases of dystrophia myotonica. Klein (1958) found a high arched palate in 40% of his cases. This was present in Case 6.

Bodily Dyscrasia.—A generally wasted appearance, premature baldness, cataracts, and testicular atrophy are features of the disease in adults. The three older children had this wasted appearance and were below the third percentile in weight, though only Case 3 was below the tenth percentile in height. Cataracts have not been detected, but slit-lamp examinations were carried out only in Case 6. Cases 1 and 3 have a receding hairline. The three male children have apparently normal testicles, except that in Case 5 one is undescended.

Speech.—In adults this may become slow, nasal, and indistinct from a combination of facial, palatal, and lingual weakness and/or myotonia. In the five older children speech has been delayed, and in three it is nasal in quality.

Mental Equipment.—Dystrophia myotonica is often associated with defective intelligence. It has been suggested that a severe form of the disease with oligophrenia is the extreme manifestation of the responsible gene. The evidence in favour of a dementing process, however, is less overwhelming. Maas and Paterson (1937) studied 29 cases and found 17 to be of low intelligence. In 11 the intellectual defect had been present since childhood and apparently before the obvious onset of the disease. The others seemed to show evidence of dementia. Those with severe muscle-wasting were the most seriously affected intellectually. Disorders of affect are said to occur, ranging from lack of energy and initiative to complete inertia. One wonders, however, in how many cases this impression is conveyed by oligophrenia combined with physical disability. Estimate of mental age is particularly difficult in young children affected with dystrophia myotonica because retarded speech and motor development can be attributed to physical handicap. Error may result from interpreting the lack of facial expression as evidence of mental retardation (Evans, 1955). Of the older children, one (Case 1) attends an occupation centre, one (Case 2) attends a school for the educationally subnormal, and (Case 3) had an I.Q. of 60 at 8 years. Only in Case 4 have repeated intelligence tests been carried out. He has been seen five times over the past four years by the same educational psychologist (Mr. L. Gardner). During this period there has been a steady fall in his verbal I.Q., so that betwen 6 and 10 years it has fallen by 15 points. It is not easy to interpret this apparent deterioration, but the number of tests carried out and the steady fall militate in favour of this being a true fall in I.Q.

Course and Prognosis

In adults the onset is usually insidious and deterioration slow. We know that sometimes an adult history goes back to infancy. The immobile face and sucking difficulty dating from birth seem to indicate that the degenerative process started *in utero*. In Case 6 there was marked wasting of the temporal muscles at 9 months; if, as seems likely, this was present to some degree at birth, then these muscles, too, started degenerating *in utero*. The same comments apply to the presence of talipes in these children. We know that on occasion in adults localized muscle-wasting can be remarkably rapid at the onset without the disease progressing further at the same speed (Klein, 1958, Case 53). None of our cases have been followed up long enough for an accurate assessment of the course in childhood. Only in Case 2 has clear evidence of deterioration been shown. The others, while being slow to develop skills, have nevertheless continued to improve in performance. The dubious mental deterioration in Case 4 is discussed above.

Family History and Mode of Inheritance

Dystrophia myotonica is inherited as if due to a dominant gene with variable manifestations. The disease is said to show "anticipation" in that the children are affected at an earlier age than are the parents and there is an increase in severity in succeeding generations. This is almost certainly due to the tendency for the more mildly affected individuals of one generation to transmit the gene to the next generation; on the whole the severely affected do not bear children.

It is noteworthy that the affected parent in all our cases is the mother and that with one exception she has minimal features of the disease. Maas (1937) has remarked on the greater number of women with a mild form of the disease, but Klein's (1958) figures suggest that transmission is commoner through a mildly affected father. In two of the families here reported, the mother's brother is severely affected. Caughey and Brown (1950) have pointed out that females do not exhibit the striking hypogonadism obvious in males with dystrophia myotonica.

The genetic problem is well reviewed by Thomasen (1948) and Klein (1958).

Ancillary Aids in Diagnosis

Electromyogram.—This is the only investigation likely to provide diagnostic proof if there is clinical doubt. It may of course, at some stage and in some muscles, be normal, as it was in Case 5 at 14 months. In Case 6 at 9 months, it provided conclusive proof of myotonia even though this was not evident clinically. Depending on the stage of the disease and the muscle tested, it may show at rest the grouped, repetitive high-frequency discharges and "myotonic dive" of myotonia or on volition the myopathic pattern of a muscular dystrophy. Both changes may of course appear in the same muscle.

Serum Aldolase.—This has been normal or slightly raised as in adults (Evans and Baker, 1957; Pearson, 1957).

Urine Creatine and Creatinine Coefficients.—As in other muscular dystrophies the creatine may be raised and creatinine reduced. This was the case in the two children on whom the test was carried out.

Skull X-ray Examination.—This was normal in two children at the ages of 14 months and 6 years respectively. The brother and sister (Cases 2 and 3) have small pituitary fossae, and Case 2 has some thickening of the calvarium; Case 1 has a small pituitary fossa and large frontal sinuses. At 6 years Case 4 had a normal skull *x*-ray picture, but by the age of 10 years this showed thickening of the calvarium. The changes noted in adults are: small pituitary fossa, thickening of the calvarium, internal hyperostosis of frontal and parietal bones, enlarged sinuses (Caughey, 1952).

E.C.G.—This was normal in the two children tested. The commonest abnormality reported in adult cases has been prolongation of the P–R interval and QRS complex (Fisch, 1951).

Muscle Biopsy.—This was carried out in one case only, but failed to show "diagnostic features" of dystrophia myotonica. These are thought to be enlargement of scattered muscle fibres and the presence of long rows of centrally placed sacrolemmal nuclei in otherwise normal muscle fibres. Other changes consistent with a muscular dystrophy may occur (Adams *et al.*, 1953).

Urinary Excretion of 17-Ketosteroids.—These have been reported as below normal in adults (Caughey and Brown, 1950). Estimations have not been carried out on our cases.

Discussion

Amyotonia Congenita Syndrome.—Early in life all these children presented as "floppy infants" backward in motor and later in speech skills. The possible causes of infantile flaccid paresis are numerous (Walton, 1957). Broadly speaking, those children who show steady progress are likely to be examples of benign congenital hypotonia. Much more rarely the very early onset and remission of polyneuritis or polymyositis may follow a similar course. As a rule one is justified, on seeing a limp and floppy child steadily acquiring new skills, in giving a good prognosis. Dystrophia myotonica is an exception to this generalization. All our cases have continued to acquire skills in early childhood, but, of course, they carry the eventual prognosis of the progressive disease. A history of difficulty with sucking, facial paresis, and possibly club-feet should make one search further for signs of dystrophia myotonica in the infant and his parents.

Möbius Syndrome or Congenital Facial Diplegia Syndrome.—Most cases are probably due to a congenital defect of muscle (Evans, 1955). Congenital facial diplegia has been described as occurring in combination with weakness of external ocular muscles, masseters, or muscles of the palate, pharynx, larynx, or tongue (Henderson, 1939; Evans, 1955). It has been personally observed, moreover, with sternomastoid weakness and wasting of the temporal muscles. Four cases of this syndrome, which illustrate certain similarities between it and dystrophia myotonica, are briefly reported in Appendix I. One patient (Case D) is of particular interest in this connexion: she had palatal and facial paresis dating from birth, while her father has the facies of dystrophia myotonica and a myotonic reaction on thenar percussion. This child is being closely watched in case she develops any signs of dystrophia myotonica herself. Children with facial diplegia do not usually show universal hypotonia, but in Appendix II three brief case reports are given which indicate that this may occur. They also illustrate the similarity with the early clinical picture of dystrophia myotonica in infants. The individual muscles mentioned are weak out of all proportion to the general muscular feebleness. Congenital talipes, which not uncommonly occurs in combination with Möbius syndrome, has been present in three of the six children with dystrophia myotonica.

Differential Diagnosis in Older Children.—These children are likely to be seen (often in orthopaedic clinics) because of residual talipes deformities, difficulty in walking, or postural defects. At this age many stigmata of dystrophia myotonica may be present. Peroneal muscular atrophy, myopathy, amyotonia congenita, and even a progressive bulbar palsy may all be considered unless the distinctive features of dystrophia myotonica are noted.

Summary

Six cases are reported of children with dystrophia myotonica whose symptoms date back to early infancy. The youngest in whom the diagnosis was made was aged 9 months.

These case reports illustrate that the onset of dystrophia myotonica may be earlier than is generally recognized, that dystrophia myotonica is occasionally responsible for the syndrome of amyotonia congenita (Oppenheim's syndrome); and that dystrophia myotonica is occasionally responsible for the presence of congenital facial diplegia.

Four case histories are briefly outlined in Appendix I because they illustrate certain similarities between dystrophia myotonica and Möbius syndrome).

Three case histories are briefly outlined in Appendix II because they illustrate similarities between dystrophia myotonica and facial diplegia occurring as one feature of benign congenital hypotonia.

The clinical features of dystrophia myotonica in childhood are outlined and the use of ancillary aids in diagnosis is mentioned.

APPENDIX I. CONGENITAL FACIAL DIPLEGIA ASSOCIATED WITH WEAKNESS OF CERTAIN OTHER MUSCLES

Case A.—Boy now aged 12. Facial diplegia, bilateral external rectus paresis, left sternomastoid atrophic and weak, poor palate movement, unilateral talipes. Not a floppy infant; milestones of development normal except speech.

Case B.—Boy now aged 11. Facial diplegia; weak masseters, temporal muscles, and sternomastoids; wasted tongue. Generalized poor muscular development, but not a floppy infant and milestones of development normal.

Case C.—Boy now aged 7. Facial diplegia, bilateral external rectus paralysis, poor palate movement, fibrillating tongue. Unilateral talipes, with wasting of muscles of anterior compartment of lower leg and some shortening of limb. Normal electromyogram and intensity duration curves of facial, lingual, and limb muscles. Not a floppy infant. Development delayed though he has shown steady improvement.

Case D.—Girl now aged 8. Facial diplegia, palatal paresis. Father has facies of dystrophia myotonica and myotonic reaction over thenar muscles.

APPENDIX II. CONGENITAL FACIAL DIPLEGIA WITH BENIGN CONGENITAL HYPOTONIA

Case E.—Girl now aged 5. Facial diplegia, poor palate movement, bilateral talipes, delayed milestones with universal hypotonia and absent reflexes.

Case F.—Boy now aged 5. Facial diplegia, poorly developed sternomastoids, absent clavicular heads of pectoralis major, delayed milestones with universal hypotonia and absent reflexes.

Case G.—Girl now aged 11. Facial diplegia, delayed milestones with universal hypotonia and sluggish reflexes.

I am grateful to the physicians of the Hospital for Sick Children, Great Ormond Street, for permission to publish details of cases under their care, and to the department of medical illustration for the clinical photographs. I would particularly like to thank Dr. P. H. Sandifer for much helpful criticism and advice.

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"A notable innovation, now a little over a year old, is the Flying Surgeon Service sponsored by the Queensland Government. This is designed to provide surgical facilities for 21 towns in Western Queensland. Regular monthly visits are paid to 16 of these, all of which have one or more resident doctors. Towns which are without a resident doctor are visited by the flying surgeon only if the doctor of the Flying Doctor Service requests assistance with a patient who needs a surgical opinion or operation and cannot be moved. The service is provided by a surgeon, an anaesthetist, and a pilot, all based on Longreach, which is approximately in the centre of the area. The hospitals in the scattered towns are equipped with routine surgical instruments and materials, but the flying surgeon brings with him whatever else is needed in the way of instruments and equipment. The anaesthetist carries a portable anaesthetic machine. . . . The service is essentially consultative, as patients are seen only at the request of another doctor. If the flying surgeon considers a surgical operation necessary he may recommend transfer of the patient to a larger and better-equipped centre, he may perform the operation with the resident doctor as assistant, or he may act as assistant while the resident doctor operates." (*Med. J. Aust.*, October 15, 1960.)

GASTRIC TUBERCULOSIS

BY

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Tuberculosis of the stomach is a rare disease. Palmer (1950) has estimated from previously published material that 159 cases were found among 96,251 necropsies (0.16%) and 117 among 20,585 necropsies on subjects whose primary disease was tuberculosis (0.57%). He states further that 19 instances of tuberculosis were found among 17,542 specimens obtained from stomach operations (0.1%).

The diagnosis is difficult to establish clinically, and the condition may be confused with peptic ulcer and with neoplasm of the stomach. Accordingly, the following case seems worth recording.

Case Report

The patient, an Indian aged 45, was first seen in hospital in 1951, complaining of epigastric pain, lethargy, and loss of weight. He had come to Glasgow from the Punjab in 1948 and had worked as a manual labourer. His knowledge of English was limited. Abnormal findings on physical examination were epigastric tenderness and slight enlargement of cervical, axillary, epitrochlear, and inguinal lymph nodes. No abnormality was found clinically in the lungs, but radiographic examination showed a small area of opacity in the right upper lung field, thought to be due to primary tuberculous infiltration. Tubercle bacilli could not be found in the sputum. E.S.R. was 65 mm. in one hour (Westergren). Haemoglobin was at first 12.1 g./100 ml., but during the next two weeks a moderate degree of anaemia developed from loss of blood into the gastro-intestinal tract. Faecal occult blood tests were repeatedly positive. Neither ova nor cysts could be found in the stools. Blood W.R. was negative. Barium-meal examination revealed nothing abnormal. Orthodox medical treatment for duodenal ulceration was given and the symptoms subsided. The haemoglobin and E.S.R. returned to normal in three weeks. The patient was discharged on an ulcer regime. He was asked to attend the follow-up clinic for review and further chest *x*-ray examination, but did not do so.

In 1954 he was again admitted to hospital with post-prandial epigastric pain and frequent vomiting. Barium-meal examination showed evidence of active duodenal ulceration; there was no sign of pyloric obstruction. This examination was repeated two months later with the same findings. A normal acid curve was obtained by fractional test meal. Slight pleural thickening was seen over the upper part of the right lung on the chest *x*-ray film. This has persisted unchanged on subsequent radiographs. E.S.R. was normal. Again there was a good symptomatic response to medical treatment for peptic ulcer.

He had a similar episode in 1955. In 1956 he was in the medical unit of the hospital for three periods of several weeks with epigastric pain and vomiting. Barium-meal examination again showed signs of duodenal ulcer. The intervals of relief produced by strict ulcer regime with bed rest became progressively shorter and surgical treatment was at length undertaken.

Operation (Mr. F. Smith).—On September 13 a hard ulcer crater penetrating the pancreas was found in the pylorus.

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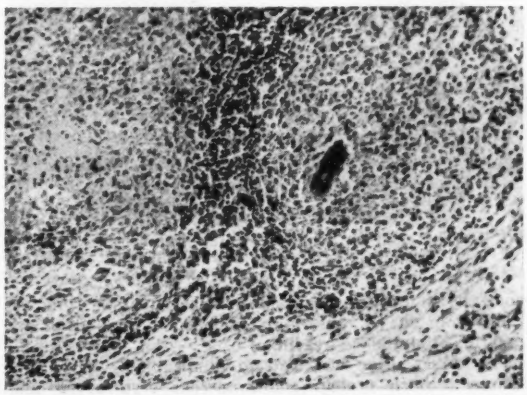
Small firm white nodules were present on the surrounding serous surfaces and near-by omentum. The liver and rest of the peritoneum looked normal. Anterior Polya-type partial gastrectomy, with Hofmeister valve and complete excision of greater and lesser omenta, was performed.

Pathological Findings.—The pathological report (Dr. H. McDonald Cameron) on the gastrectomy specimen was as follows: "Partial gastrectomy specimen in which there is a small simple ulcer 5 mm. in diameter in the pylorus. Histologically, the ulcer seems to be of indefinite outline and is floored by granulation tissue containing large masses of plasma cells and lymphocytes and focal collections of polymorphs. The muscularis mucosae is in part lost in the inflammatory reaction, and in part replaced by fibrous tissue. Lying on both sides of this layer there are well-formed epithelioid tubercles containing giant cells of Langhans type. There is extensive irregular fibrosis of the muscle coats, and tubercles are found throughout these and as far as the serous surface. A few tubercles show central necrosis. No acid-fast bacilli are seen in the Ziehl–Neelsen preparation and no inclusion bodies are found in the giant cells (see Fig. 1). A portion of omentum submitted separately shows similar changes. While it is conceivable that this is a tuberculoid reaction to foreign material in the ulcer, it is more likely to be tuberculous, and, in spite of the unusual site, could justify the diagnosis of tuberculous ulcer of the stomach."



Section of tissue removed from the stomach at operation, showing epithelioid tubercle with giant cells of Langhans type and central necrosis.

Tubercle bacilli could not be found in specimens of sputum, in gastric washings, faeces, or in the operation specimen.

The patient was discharged from hospital in November, 1956, and advised to continue on an ulcer regime. Again he failed to return for follow-up examination, and was not seen at the hospital until December, 1958, when he was readmitted to the medical unit because of epigastric discomfort and painful swellings in his neck. His voice was hoarse. Physical examination showed epigastric tenderness and marked, firm, discrete enlargement of cervical, axillary, epitrochlear, and inguinal lymph nodes.

No abnormality was found in the urine. E.S.R. was 13 mm. in one hour (Westergren), blood count was normal. Blood W.R., Paul–Bunnell test, and agglutination reactions against typhoid and abortus organisms were negative. Biopsy of an enlarged cervical lymph node was reported on by Dr. Cameron as follows: "Enlarged lymph node, 2.5 by 1.5 by 1 cm. It consists of dense white tissue with several irregular areas of necrosis. Histologically it shows typical caseating tuberculosis. Scanty acid-fast bacilli are seen in the Ziehl–Neelsen preparation. This finding lends considerable support to the suggestion that the gastric lesion was truly tuberculous."

Barium-meal examination showed a well-functioning stoma and no other abnormality.

Laryngoscopy and bronchoscopy (Dr. A. Lees) were negative. *X*-ray examination of the chest showed only the previously noted evidence of pleural thickening. Mantoux test (1/10,000 O.T.) was strongly positive. No tubercle bacilli could be found in sputum or faeces. In one specimen of gastric washings acid- and alcohol-fast bacilli were found on the film (Ziehl–Neelsen); cultures and guinea-pig inoculations were negative.

The patient was again given orthodox medical treatment for peptic ulcer, and from December 20, 1958, streptomycin 1 g. daily, by intramuscular injection, and isoniazid, 100 mg. b.d. by mouth. After five days the isoniazid was increased to 100 mg. t.i.d. At that time he became increasingly querulous and resentful of his treatment regime. Partly because of language difficulty, the degree of mental upset was underestimated. On January 2, 1959, he jumped from a first-floor window and was unconscious for 15 minutes. He sustained a compound fracture of his right humerus. A week later he went as a voluntary patient to a mental hospital.

During the next few months he had episodes of depression and excitement and was at times hallucinated. He was given chlorpromazine 200 mg. t.i.d. and had electric convulsion therapy. Streptomycin 1 g. daily was continued until May 26. He had no dyspeptic symptoms after February, 1959, and a month later there was no detectable lymph-node enlargement. He gained weight. The remission of physical symptoms has continued up to the time of writing.

Discussion

The diagnosis of gastric tuberculosis in this case is based on the histological findings in the operation specimen, the presence of active tuberculosis in the lymph nodes, the recurrence of dyspeptic symptoms after operation, and the disappearance of both dyspepsia and glandular enlargement after antituberculous chemotherapy. Tubercle bacilli were not found in the sections of gastric tissue. However, according to Toole and Propatoridis (1950), Groders found that the presence of tubercle bacilli could be demonstrated in operation specimens in only about a third of the cases of gastric tuberculosis.

There do not seem to be any distinctive clinical features of tuberculosis of the stomach. An active tuberculous focus elsewhere in the body may arouse suspicion, but does nothing to prove the nature of the lesion in the stomach. Barium-meal examination may suggest the diagnosis by such findings as simultaneous involvement of the stomach and duodenum in ulceration, a fistulous track, or the presence of peristaltic waves passing through what seems to be extensive malignant infiltration of the stomach (Gaines *et al.*, 1952). Tuberculosis of the stomach may explain the presence of achlorhydria and hypochlorhydria with evidence of ulceration. Tubercle bacilli may be demonstrated in the gastric juice, but if there is coincidental pulmonary tuberculosis the interpretation of this finding may be difficult. As has already been mentioned, histological appearances may not be conclusive.

If the diagnosis of gastric tuberculosis is made without laparotomy, orthodox medical treatment for peptic ulcer and antituberculous chemotherapy may lead to cure. Probably more often the diagnosis will be made in life by histological study of operation specimens, and chemotherapy will then be considered as additional treatment. It seems likely that our patient would have made better progress if antituberculous therapy had been given when partial gastrectomy disclosed the diagnosis.

This comment may apply to other cases of the disease, even in the absence of any overt sign of another tuberculous focus.

Summary

A case of tuberculosis of the stomach is described.

The diagnosis was made from the histological study of tissue removed by partial gastrectomy, undertaken because of intractable abdominal pain, which recurred after operation.

Two years later the patient developed a psychotic state after two weeks' treatment with streptomycin and isoniazid, given because of tuberculous adenitis and abdominal pain.

The abdominal pain and enlargement of lymph nodes subsided after two months' antituberculous chemotherapy.

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Medical Memoranda

Cantharidin Poisoning Due to a "Blister Beetle"

The properties of cantharidin and its occurrence in "Spanish flies" and widely distributed genera of "blister beetles" (*Mylabris, Epicanta, Cyanolytta,* and *Cercoctis*) are recognized by orthodox toxicologists and by witch-doctors in some African countries (Gelfand, 1948; Gordon, 1943; Hinman, 1933), but the apparent rarity of accidental poisoning by percutaneous absorption of this substance warrants the publication of the following history.

Case Report

An African male child aged 22 months and weighing 22 lb. (10 kg.) was brought to the Leprosy Research Unit Clinic, Uzuakoli, in January, 1960, with the complaint that blebs had appeared suddenly on his hands and face and that he was passing, frequently and painfully, small quantities of blood-stained urine.

As these symptoms suggested cantharidin poisoning (Nickolls and Teare, 1954; Craven and Polak, 1954), the mother was asked if she had seen any "Spanish flies" (*Lytta vesicatoria L.*) near the house. She denied having seen any such "flies," but recounted that the previous day her child and several older companions had "raced" some brightly coloured beetles one against the other, returning them to the starting-point after their noisy short-range flight. The patient had apparently, in a fit of pique, torn his losing beetle to pieces.

He had run crying to his mother, holding his left hand in pain, but since she could see no sign of sting or bite she discounted his story. He refused food and lay down, but soon awoke screaming. Large blebs had made their appearance on the fingers of the left hand and on the lower lip and adjacent gum. Two hours later blebs appeared on the chin (Fig. 1).

During the night further blebs appeared on the dorsa of both hands and on the neck, and the child passed urine involuntarily several times. (He had achieved bladder control, and normally passed no urine at night.) On each occasion he screamed with pain, especially towards the end of the act. He was at first fretful, but towards morning became quite deeply stuporous, rousing partially only when passing urine. In the light of day the mother noticed that the under-sheet, wet with urine, was stained red, and in alarm brought the child to hospital.

Tense blebs were seen on the fingers of both hands, mainly the left. (The child seemed to be right-handed, but had clutched the dismembered beetle in the left hand.) Blebs were also present on the chin, lower lip, and adjacent gingival mucosa. No lesions were seen beyond the gum. A line of smaller vesicles ran across the right anterior triangle of the neck. The red, hot skin surrounding the blebs was tender on gentle palpation.

During the examination the sleeping child flexed the thighs on the abdomen and screamed. A small quantity of blood-stained urine was voided, followed by a few drops of bright-red blood. No other abnormalities were revealed on routine clinical examination. The pulse and temperature were normal.

The mother then indicated two similar bullae on her own skin, on the inner aspect of the right thigh just above the knee. She had not to her knowledge been in contact with a beetle, though she imagined that her child's soiled hands

Fig. 1.—The child on admission.

Fig. 2.—Internal aspect of the mother's thigh just above the knee.

might have touched her skin in that situation (Fig. 2). (Fluid from one of those bullae, applied to the skin of my forearm, produced no reaction.)

The child's urine was acid to litmus; S.G. 1008; and contained much protein and numerous erythrocytes and leucocytes, in proportions similar to those of whole blood. No ova were seen (vesical schistosomiasis does not occur in this district), and no organisms were found on examination of the fresh specimen or after staining. No casts were seen.

The blood showed a leucocytosis of 12,300 cells per c.mm., neutrophils accounting for 64%, lymphocytes for 31%, monocytes for 3%, and eosinophils for 2%.

The faeces, though macroscopically normal, contained numerous erythrocytes.

Treatment.—As the severe toxic action of cantharidin on the glomeruli of the rabbit kidney is said to be prevented by alkalinization of the urine (Dixon, 1925), the child was given adequate alkalis by mouth. Calamine lotion was applied to the bullae and surrounding skin, and the lips and gums were bathed frequently with an aqueous solution of acriflavine.

Progress.—During the three days after admission the patient's general condition improved slightly, though he continued to be abnormally drowsy. The urinary symptoms persisted unchanged: at least eighteen involuntary voidings of blood-stained urine were counted in the twenty-four hours. At the end of some acts, clotted blood and stringy blood-stained mucus were passed. The bullae on skin and mucosa increased in size, coalesced, and then burst, leaving ulcers with a dirty sloughing base and ragged edges. During this period the white cell count decreased to 10,500 and 10,600 cells per c.mm., with 51% and 41% of neutrophils respectively. The urine became and remained alkaline in reaction. After the third day the quantity of protein in the urine and the number of erythrocytes began to diminish,

but it was not until the ninth day after the onset of symptoms that the urine became normal. No casts were ever found. By that time the ulcers had all healed. The white cell count returned to normal, and the faeces no longer contained blood. The blood urea was 16 mg./100 ml.

Investigations.—After the initial clinical examination of the child, search was made in the family compound for the remains of the beetle that the child had torn apart: fortunately, these were all found. They were dispatched (by air) together with whole live specimens of beetles with the same, and with different, markings to the British Museum, Natural History, where they were kindly identified by Miss C. M. F. von Hayek, Senior Scientific Officer. The dismembered beetle was *Mylabris bifasciata De G.*, and the others were *Mylabris trifasciata Thunberg* (Coleoptera, Meloidae).

All Meloidae are said to contain cantharidin, which is present in the haemocoele as well as in the elytra and genitalia and joint fluid (Craig and Faust, 1951; Patton and Evans, 1929). According to Gordon (1943), South African Meloidae contain more cantharidin weight for weight than does the "Spanish fly."

Our personal observations are in accord with generally reported findings that the number of such beetles varies within wide limits: sometimes none can be found; at other times they are very numerous. January is in the dry season here, with the dust-laden harmattan blowing from the north.

Comment

Noteworthy features of the incident are: (1) The brief interval between the handling of the fragmented beetle and the onset of symptoms: pain occurred at once, and the first blebs appeared within 30 minutes; (2) the toxic principle seems to have been absorbed through the intact skin and labial mucosa; it is improbable that any part of the beetle was actually swallowed; the absence of symptoms of gastric irritation and of altered blood in the faeces suggests that the erythrocytes present indicate a toxic action during elimination of the cantharidin into the lower bowel; (3) the absence of symptoms in the children who handled intact live beetles; (4) the localized manifestations of cantharidin irritation in the mother's skin, presumably mediated by deposits on the child's fingers; (5) the severity and long duration of the strangury and haematuria after percutaneous absorption of a necessarily small amount of toxin; (6) the persistence of the haematuria despite adequate alkalinization of the urine; (7) the complete recovery of the child.

My grateful thanks are due to the Permanent Secretary, Ministry of Health, Eastern Region, Nigeria, and the Director of Medical Services, Dr. S. E. Onwu, M.V.O., C.B.E., for permission to publish, and to Miss C. M. F. von Hayek, Senior Scientific Officer, British Museum, Natural History, for kindly identifying the beetles.

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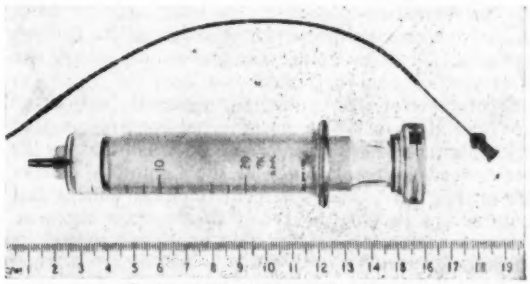
A Technique for Operative Cholangiography

Operative cholangiography is a valuable adjunct to biliary surgery. Its acceptance as a routine operative investigation depends upon the technique being simple, with the minimum of additional manœuvres, and not time-consuming. The following technique has been evolved and used in 23 consecutive cases with production of good *x*-ray plates and the avoidance of an unnecessary exploration of the common bile-duct.

The removing and replacing of towel clips during the filming can be avoided by stitching the towels together with a linen thread on a Colt needle, and stitching the tetracloths to the peritoneum and transversus abdominis muscle in a similar manner.

A bulb ureteric catheter, which has been cut down to about 12 in. (30 cm.) in length, is connected to a 10-ml. syringe with a blunt needle which fits snugly (see Fig.).



Bulb ureteric catheter and syringe.

Air is expelled from the catheter by pushing a few drops of the "hypaque" through the catheter before it is brought near the operation site. The common and hepatic bile-ducts are defined and the cystic duct is made taut by traction on the gall-bladder. A suture is placed around the cystic duct and a small slit made in its side with scissors approximately half-way along its length. The bulb end of the catheter is then introduced into this slit and eased into the common bile-duct. The suture is then tied tightly around the catheter over the cystic duct. The ends of the suture are left long but are not clipped. The catheter is then withdrawn slowly until the bulb portion impinges against the ligature and thus fits tightly with no fear of the catheter being pulled out accidentally during the removal of the retractors, swabs, and the assistant's hand prior to injection. Ideally, the table is tilted through 15 degrees to the right to ensure that the bile-ducts are not superimposed over the vertebral column on the film; if the table does not have a lateral tilt the *x*-ray tube should be placed at an angle of 15 degrees to overcome this superimposition. Bile is withdrawn into the syringe to ensure that no air bubbles have been introduced into either the catheter or the ducts. Approximately 7 ml. of hypaque is then injected slowly and the film taken. While the film is being developed the appendix can be removed without fear of the catheter slipping out, as further films may on rare occasions be required.

To remove the catheter, a second suture is placed around the cystic duct, between the first ligature and the junction of the cystic and common hepatic ducts, but it is not tied. The ligature retaining the catheter is cut with a small knife. The catheter and the cut ligature are removed and the new suture is tied around the cystic duct between the "slit" and the common duct.

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Reviews

CLINICAL GASTROENTEROLOGY

Clinical Gastroenterology. By F. Avery Jones, M.D., Hon.M.D.(Melbourne), F.R.C.P., and J. W. P. Gummer, M.S., F.R.C.S. (Pp 652+vii; illustrated. 70s.) Oxford: Blackwell Scientific Publications. 1960.

One of the most certain ways to success in medicine is to write a good textbook on general medicine or one of its major subdivisions. It is therefore surprising that until now we should have had no British textbook of gastroenterology and no outstanding American one apart from Bockus's three-volume work published 1943–6. This is partly because there have been no major discoveries in gastroenterology such as have changed the landscape in diseases of the heart and the lungs and have stimulated people to write new guides to these subjects. Gastroenterology has grown only slowly like a coral reef. Another factor has been the dispersion of the school of gastroenterology which Hurst built up at Guy's Hospital. The omission has been repaired by Avery Jones and Gummer, whose book is based on the practice of gastroenterology at the Central Middlesex Hospital. The special gastroenterological unit at this hospital has become deservedly famous as a centre of research and teaching, and this book will extend its reputation.

The book begins with the discussion of symptoms, functional disorders, and disorders of motility. Then come torsion and volvulus, congenital anomalies, and diverticulosis. Trauma, vascular disorders, tumours, and hiatus hernia follow next, and lead on to the hard core of digestive disorders—peptic ulcer and alimentary bleeding, steatorrhoea, regional ileitis, and ulcerative colitis. Diseases of the pancreas and the peritoneum are included, but not diseases of the liver, because the book is meant to be a companion volume to Sheila Sherlock's *Diseases of the Liver and Biliary System.*

The main emphasis is on diagnosis and management, and as the authors are respectively physician and surgeon there is no false antithesis between medical and surgical treatment. The allotment of space to the different parts of the subject is well planned, and the writing, though at times a little rough, is clear and explicit. Ample references are given to the key papers and the recent literature. There is a tendency in the earlier part of the book to give rather too many lists of such things as aetiological factors, or questions a patient may be asked. The list of causes of functional and organic indigestion, for example, is so long as to be unhelpful, for one can hardly imagine asking oneself, Has the patient got (*h*) pregnancy, (*i*) pernicious anaemia, or (*j*) duodenal diverticula? One would gladly exchange these lists for more of the authors' stimulating personal observations such as the following: "There are three medical diseases which particularly may bring the patient complaining of constipation to the doctor and should be kept in mind. These are myxoedema, depression and diabetes."

The book is magnificently illustrated with a wealth of *x*-ray pictures, which are well reproduced. These have entailed using a shiny paper, which makes the book heavy in the hand, but one cannot have it both ways. There is a good index. The authors have produced a book that was badly needed and that fills a gap in the literature, and there is little doubt that it will become the standard textbook of gastroenterology in this and other English-speaking countries.

L. J. Witts.

SCHOOL HEALTH PIONEER

Margaret McMillan: "The Children's Champion." By G. A. N. Lowndes, M.C., B.Litt., J.P. (Pp. 110; illustrated. 15s.) London: Museum Press, Ltd. 1960.

Mr. G. A. N. Lowndes has compiled an excellent account of Margaret McMillan, subtitled "The Children's Champion," to celebrate the centenary of her birth. The Nursery School Association, which she founded, asked 25 people to write a personal appreciation, and the author of this biography has most skilfully arranged extracts and certain other passages from published work to give a picture of this remarkable woman. Born in America of Scottish parents and originally trained for a career as an actress and teacher, she, together with her sister Rachel, effected a revolution of thought and action for the care of the young child. Brought back to Inverness on the death of her father in 1865, it was not until 1892 that Margaret McMillan got caught up in the social revelations of the great dock strike, and the following year she accepted an invitation to Bradford. There she began a battle for the child—school baths, medical inspection, school meals, clinics, and open-air schools. The scandal of child labour deeply affected her. With Dr. Kerr as the newly appointed school medical officer she took a prominent part in getting something done. Later, when she came back to London, it was the same story. With personality and drive, aided by her sister Rachel, she got a health centre started and from there moved on to true preventive work in open-air facilities and the now famous nursery schools. She was fortunate in her backers, but without her it might have been long years before the valuable opportunities for improving the health of the school child would have been fully realized.

Alan Moncrieff.

FACTS ON HOMOSEXUALITY

A Minority. A Report on the Life of the Male Homosexual in Great Britain. By Gordon Westwood. (Pp. 216+xii. 30s.) London: Longmans. 1960.

This is a valuable study of one hundred and twenty-seven self-confessed homosexuals, giving detailed factual information about their family background, social behaviour, and sexual activities. The method used was that of the interview. In the author's opinion, though the sample does not adequately represent all people who commit homosexual acts—the "facultative" homosexual and certain bisexual individuals may be under-represented, as also the paedophiliac or "child molester"—it is representative of those individuals who perform by far the greater proportion of homosexual acts. The author also points out that most of the literature on homosexuality has been derived from the study of two minority groups amongst homosexuals—namely, those who have received psychiatric treatment and those who have come up against the law; and these two groups are likely to be psychiatrically abnormal, or lacking in discretion, or both. Only a small percentage of the group studied had received psychiatric treatment or been convicted; and since this is also true of

the vast majority of homosexuals, this sample is more likely to be more truly representative of the average homosexual in Great Britain than is any other series previously studied.

The findings are set out with care, clarity, and modesty. It is possible to mention only a few of them. For example, the finding that 30% came from "apparently undisturbed backgrounds" cannot readily be squared with the many theories that suggest that a distorted relationship between a boy and his parents is the main causative factor in the development of homosexuality. The author's findings confirm the view that the effects of seduction and early sexual experience with adults have been exaggerated. The number with relatively sustained love affairs is higher than that usually recorded in the literature, the explanation proffered being that homosexuals with stable affairs are less likely to come into contact with the law or to seek psychiatric help. Most of the subjects led useful and productive lives; the least satisfactory personalities in this way were the most promiscuous. Most homosexuals go unrecognized by the general public; they are not effeminate pansies in appearance and are not sexually attracted by the type. Less than one-third of this group regularly had anal intercourse; there was no evidence that those that did practise buggery were worse types or in any way different from other homosexuals. (The legal penalties for buggery are, of course, vastly different from those awarded for other types of homosexual acts.) Very few adult-seeking homosexuals are sexually interested in prepubertal boys, and paedophiliacs appear to be quite a separate group.

As Sir John Wolfenden writes in the foreword: "Within its deliberate limits this survey seems to me to be excellent." Mr. Westwood is to be congratulated upon a notable contribution to the subject. It is good to learn that these researches will continue with the backing of the Home Office under the auspices of Birkbeck College, London University. In a subject so contaminated by emotion and afflicted by such a surfeit of speculation, it is as refreshing as it is rare to be provided with such a mass of facts about such matters as early family background, professional occupations, frequency and type of homosexual behaviour, heterosexual interests, and adjustment to society. The book is well written and contains an admirable bibliography.

DESMOND CURRAN.

HUMAN PROTOZOOLOGY

A Short Synopsis of Human Protozoology and Helminthology. By L. R. S. Macfarlane, O.B.E., M.D., M.A., D.P.H., Brigadier. Illustrated by R. M. Leach, B.E.M. (Pp. 251+vii; illustrated. 35s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

The parasitic protozoa and helminths of man are described in 24 chapters, which are largely based on Faust and Russell's *Clinical Parasitology*. Each organism is considered separately under the following headings: distribution, morphology, habitat, life cycle, mode of infection, pathology, symptoms, diagnosis, and curative (but not preventive) treatment. The list of parasites affecting man is almost complete, and includes the rarest helminths. A short appendix describes clearly the staining of blood films for the demonstration of parasites (including microfilariae) and some methods used in the identification of protozoa found in the faeces. A glossary of lesser known terms is more useful for the etymology of the words than for their actual meaning, which is often not the same, or is at least modified—for example, trophozoite, xenodiagnosis, karyosome, coprozoic.

Sixty-one line drawings, comprising diagnostic tables, morphological details, and schematic life histories, and eight colour plates, illustrate the text. Nearly all are original, and are the work of R. M. Leach, of the Royal Army Medical College. They are well drawn and form an important part of the book. Unfortunately the magnification is omitted.

In subsequent editions of this handbook it would be advisable for the author to check the exact wording and nomenclature of his zoological definitions, in which there are at present many inaccuracies. For example, in the class Sporozoa or in the genus *Plasmodium*; also throughout the book the usual zoological conventions are ignored and scientific names remain unitalicized, chromatin is used as a synonym for nucleus, etc. Apart from such naivetés and various ambiguities, there are serious mistakes, such as the statement that clumps of chromatin are characteristic of the *P. falciparum* schizont. A little book summarizing parasitology for the student is a recognized need, and in a corrected form this synopsis could prove invaluable.

P. C. C. GARNHAM.

VARICOSE VEINS

On the Causation of Varicose Veins and Their Prevention and Arrest by Natural Means: An Evolutionary Approach. By T. L. Cleave, M.R.C.P.(Lond.) Foreword by Harold Dodd, Ch.M., F.R.C.S. (Pp. 32. 7s. 6d.) Bristol: John Wright and Sons, Ltd. 1960.

It is always a pleasure to see original thought and work coming from the Services, where conditions are often of necessity unfavourable for clinical research. Surgeon-Captain Cleave has already applied the evolutionary approach to coronary disease. In this new monograph, on the causation of varicose veins, he proposes the argument that "the *sole* primary cause in every case is a delayed passage of colonic contents, due to the removal of fibre from the food," leading to pressure by the colon on the iliac veins. He is not the first writer to advance this simple mechanistic explanation of a complex haemodynamic problem, and some surgeons who have their daily business in the lower abdomen may decline to agree with him. Nevertheless, the discussion is so well and persuasively written, and contains such a wealth of ingenious reasoning, that it has a valuable function in stimulating further thought on an unsolved problem to which animal experiment is not applicable. It would, moreover, be interesting to measure the leg venous pressures, before and after relief, of such patients as the individual (immortalized by Professor Samson Wright) who went from June 18, 1900, to June 21, 1901, without a motion.

J. H. L. FERGUSON.

ALDOSTERONE

Aldosterone in Clinical and Experimental Medicine. By E. J. Ross, M.D., Ph.D., M.R.C.P. (Pp. 144+viii. 22s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

The development of knowledge of aldosterone has been so rapid, as shown by the fact that more than 500 references are quoted in the bibliography, that an authoritative review of the subject is timely. The contents are comprehensive and include all those aspects which can be regarded as being pertinent to

the clinical endocrinologist—namely, biochemistry and physiology of aldosterone, its determinations in biological material, and its abnormalities in clinical medicine. The author's approach is scholarly and critical in the manner of specialized reviews, but his style makes it difficult sometimes for the reader to be sure where the emphasis is intended to be. This may be partly due to the fact that the text was originally a doctorate thesis and was subsequently expanded, thereby suffering from unevenness of presentation.

The discussion of Conn's syndrome is accompanied by a valuable tabular analysis of 22 cases, which are regarded as examples of the syndrome, abstracted from the literature. A particularly difficult topic is the question of the differential diagnosis of Conn's syndrome, and devotion of a little more space to this question would be helpful. The final chapter comprises a thoughtful exposition of the author's own views on the normal role of aldosterone and its part in the production of the electrolyte disturbances and oedema with which it is associated.

In the opinion of the reviewer this monograph will prove to be of most value to specialists interested in endocrinology and the kidney for reference purposes, rather than to the reader making his early explorations of this complex subject.

F. T. G. Prunty.

GROWING UP IN NYASALAND

Children of their Fathers. Growing up Among the Ngoni of Nyasaland. By Margaret Read. (Pp. 176; illustrated. 18s.) London: Methuen and Co., Ltd. 1959.

The Ngoni tribe migrated northwards from their home in Natal in the middle of the nineteenth century. They reached the shores of Lake Victoria after forty years trekking but turned south again to settle in Nyasaland. Margaret Read (not to be confused with her near-namesake anthropologist), lived for many months among the Ngoni clans in two villages—one large (122 households) and one small (31 households). In an earlier work she made a full-scale study of Ngoni culture and social organization, but in this book she has limited herself to the Ngoni family life and their way of rearing children from birth to marriage. The three individual qualities which the Ngoni most value, and which are firmly imposed on the young, are physical courage, thoroughness (not to be confused with cleverness), and wisdom in personal relations. Respect and obedience towards elders and superiors, with generosity towards equals and inferiors, are strictly enjoined. If these ideals are reminiscent of Victorian England, so are the Ngoni methods of achieving them. The children have nursemaids to look after them when their mothers are concerned with housekeeping, husbands, and the younger babies. The boys are removed at seven years of age to the male dormitory, where they remain till they enter the army. In the dormitory fagging by the smaller boys, beating as a disciplinary method, and under-feeding are practised. The young look forward to the time when they, too, will beat the fags and have enough to eat. The boys are educated in manly arts (physical combat and fencing with singlesticks) and in male pursuits, such as the care of cattle and hunting. The social code is rigid: for example, the girls who lose their virginity (they are examined every two months by a jury of matrons) are stigmatized publicly. Two features of Ngoni social organization have been adopted by the West since the days of Queen Victoria—universal military conscription and petting (love-making short of penetration is encouraged by the Ngoni). Good manners are rigorously instilled. If a child eats noisily, someone says, "I hear the guns of the Tyandla people booming," and the rebuked infant holds his head in shame. The children must never walk behind their elders but must pass in front of them, bending slightly forward, murmuring, "I am before your eyes."

These anthropological studies have great interest for those of us living in other cultures; and this book is particularly good—an admirable and well-illustrated documentary. Margaret Read, in common with those educationists who are to-day quite rightly concerned with educating their pupils for community living, exaggerates the importance for the Western world of these and similar investigations. The fact that neurosis and delinquency in adolescence are as rare amongst the Ngoni as they were amongst the Victorians does no more than demonstrate what everyone knows—that traditional ideals working through a rigid social framework stabilize (some would say petrify) society. What will happen to the Ngoni adolescent under the impact of Scottish missions, Government education, economic changes, and Nyasaland Nationalism? When "mankind is on the move" the young suffer, as they did when the Ngoni left their homes in Natal.

D. V. Hubble.

TEN THOUSAND SPINES

The Human Spine in Health and Disease. Anatomico-pathologic Studies. By Georg Schmorl, M.D. *Clinico-radiologic Aspects.* By Herbert Junghanns, M.D. First American edition, translated and edited by Stefan P. Wilk, M.D., and Lowell S. Goin, M.D. (Pp. 285+xii; illustrated. $21.) New York and London: Grune and Stratton. 1959.

This work was originally published under the title *Die Gesunde und die Kranke Wirbelsäule in Röntgenbild und Klinik* in 1932, the year of the senior author's death. Professor Schmorl, the distinguished German pathologist, was in charge of the Dresden Institute of Pathology, and in collaboration with Dr. Junghanns, a radiologist, he wrote what has become a classic monograph on the spine. In its German form it is already well known to radiologists and pathologists with a special interest in the spine, and this first English translation from the German edition of 1959 should serve an important function in bringing the work of Schmorl and his colleagues to a much wider circle of readers.

In the Dresden Institute, from 1925 onwards, the entire spine was removed intact, as part of the routine autopsy procedure; it was studied as a gross specimen and then sawn into slices for radiographic and histological study. Schmorl and Junghanns examined more than 10,000 spines in this way, and the present monograph is based on their formidable experience.

After a brief description of the normal structure and development of the spine, the book presents a systematic account of the lesions encountered in a wide variety of diseases. Osteoporosis, Paget's disease, trauma, infections, tumours, scoliosis and other deformities, "spondylosis" (osteoarthritis), and lesions of intervertebral discs are all discussed. The numerous illustrations are excellent, and outstanding are those which show the radiological appearance and the specimen photograph of the same lesion side by side. Such material greatly aids the interpretation of radiological appearances in

spinal diseases, and is, to the present reviewer, the most important feature of the book.

Less emphasis is given to histopathology, and discussions of the aetiological and metabolic aspects of the subject are not outstanding. Because of the wealth of material collected in Dresden and the meticulous care with which it was studied, it is a great pity that more detailed information is not given concerning the incidence and distribution of the various types of lesion described. A limited amount of information of this type is given for metastatic carcinoma, Paget's disease, "spondylosis," and spinal haemangioma, but even in Paget's disease—to take an example where Schmorl's work is widely known and quoted—it is not possible from the present volume to obtain information on the incidence of this condition in various age groups, or the relative frequency of involvement of the various vertebral bodies.

Schmorl was particularly interested in abnormalities of intervertebral disks and was a pioneer in their study in the years following 1925. It is therefore not surprising that the section of the book which deals with this subject is both detailed and informative.

H. A. Sissons.

BIOCHEMICAL NEUROLOGY

Biochemical Aspects of Neurological Disorders. Edited by John N. Cumings, M.D., F.R.C.P., and Michael Kremer, M.D., B.Sc., F.R.C.P. (Pp. 230+x; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

This useful book will be read by every physician interested in modern developments in neurology. Each of its twenty chapters is based on a lecture delivered at the National Hospital, Queen Square, in 1947 to 1958. The first of each pair of lectures deals with the biochemical and the second with the clinical aspects of a current topic in neuropathology. Amongst the subjects treated in this way are the vitamin-B deficiencies (Peters and Spillane), demyelination (Thompson and Symonds), porphyria (Rimington and Elkington), copper metabolism (Cumings and Kelly), and anoxia and hypoglycaemia (Richter and Williams). The biochemistry of coma, neurological aspects of liver disease, neurolipoidoses, and disorders of calcium and phosphorus metabolism and of the adrenal and pituitary glands are also discussed, and a biochemical and clinical account of muscle diseases is included.

Great care has obviously been taken to make the biochemical presentations intelligible to the clinician, and indeed the whole book is very much more readable than its somewhat formidable title would suggest. The reviewer especially enjoyed Spillane's idiosyncratically dynamic account of the vitamin-B deficiencies, with its fascinating historical vignettes; R. H. S. Thompson's clear and modest presentation of our limited knowledge in the field of enzyme disorders related to demyelination; and Sir Charles Symonds's stimulating account of the possible relationships between disseminated sclerosis and other demyelinating disorders. But such selection reflects the interests of the reader rather than the virtues of the chapters, and other readers would no doubt find other preferences amongst contributions, all of which reach a high standard. Viewed historically, *Biochemical Aspects of Neurological Disorders* is an encouraging illustration of the current escape of neurology from its nosographic preoccupations into wider and more promising fields.

Henry Miller.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Microbiology. Historical Contributions from 1776 to 1908. Edited by Raymond N. Doetsch. (Pp. 233+xi; illustrated. $5.) New Brunswick, N.J.: Rutgers University Press. 1960.

The Principles and Practice of Refraction. By G. H. Giles, O.B.E., F.B.O.A.(Hons.), F.S.M.C., D.Orth. (Pp. 688+xix; illustrated. £6 6s.) London: Hammond, Hammond and Co. Ltd. 1960.

Trance in Bali. By Jane Belo. (284+xiii; illustrated. 60s.) New York: Columbia University Press. London: Oxford University Press. 1960

Psychophysiologic Approach in Medical Practice. By William W. Schottstaedt, M.D. (Pp. 352. 60s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

Occupational Therapy in Rehabilitation. Edited by E. M. MacDonald, B.Litt., T.M.A.O.T. (Pp. 348+xvi; illustrated. 37s. 6d.) London: Baillière, Tindall and Cox. 1960.

Current Psychological Issues. Edited by Georgene S. Seward and John P. Seward. (Pp. 360. 42s.) London: Methuen and Co. 1960.

Manual for Examination of Patients. School of Medicine and North Carolina Memorial Hospital, The University of North Carolina, Chapel Hill, N.C. (Pp. 231. 34s.) London: Interscience Publishers, Ltd. Chicago: The Year Book Publishers, Inc. 1960.

Radioactive Wastes. Their Treatment and Disposal. Edited by J. C. Collins, B.Sc., M.S.E., A.M.I.C.E. (Pp. 239+xxi; illustrated. 55s.) London: E. and F. N. Spon Ltd. 1960.

The Neutron Story. By Donald J. Hughes. The Science Study Series vol. 1. (Pp. 158; illustrated. 4s. 6d.) London, Melbourne, Toronto: William Heinemann Ltd. 1960.

Magnets. The Education of a Physicist. By Francis Bitter. The Science Study Series vol. 2. (Pp. 155; illustrated. 4s. 6d.) London, Melbourne, Toronto: William Heinemann Ltd. 1960.

Soap Bubbles and the Forces which Mould Them. By C. V. Boys. The Science Study Series vol. 3. (Pp. 156; illustrated. 4s. 6d.) London, Melbourne, Toronto: William Heinemann Ltd. 1960.

Echoes of Bats and Men. By Donald R. Griffin. The Science Study Series vol. 4. (Pp. 156; illustrated. 4s. 6d.) London, Melbourne, Toronto: William Heinemann Ltd. 1960.

How Old is the Earth? By Patrick M. Hurley. The Science Study Series vol. 5. (Pp. 160; illustrated. 4s. 6d.) London, Melbourne, Toronto: William Heinemann Ltd. 1960.

Symposium on Congestive Heart Failure. Edited by Herrman L. Blumgart, M.D. (Pp. 120; illustrated. $2.) New York: The American Heart Association, Inc. 1960.

Group Processes. Transactions of the Fifth Conference, October 12-15, 1958, Princeton, N.J. Edited by Bertram Schaffner, M.D. (Pp. 196; illustrated. $4.50.) New York: Josiah Macy, Jr., Foundation. 1960.

A Short History of Obstetrics and Gynecology. By Theodore Cianfrani, M.D. (Pp. 449+xvi; illustrated. £5.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Man's Posture: Electromyographic Studies. By J. Joseph, M.D., M.R.C.O.G. (Pp. 88+x; illustrated. 44s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Lupus Vulgaris Cutis in Denmark 1895-1954. Its Relation to the Epidemiology of Other Forms of Tuberculosis. By Ole Horwitz. (Pp. 142; illustrated. $6.50.) Copenhagen. 1960.

Cold Injury. Transactions of the Sixth Conference, July 6-10, 1958, U.S. Army Medical Research Laboratory, Fort Knox, Ky. Edited by Steven M. Horvath, M.S., Ph.D. (Pp. 375; illustrated. $6.50.) New York: Josiah Macy, Jr., Foundation. 1960.

Therapeutic Meal Plans. A New Diet Manual. Edited by Ruth Gordon, Arlene Payne, and Hazel Parry. Revised edition. (Pp. 66+iii. $3.) Prepared by the Department of Dietetics and Nutrition, University of Kansas School of Medicine. Lawrence, Kansas: University of Kansas Press. 1960.

BRITISH MEDICAL JOURNAL
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THE NOBEL PRIZE

The award of the Nobel Prize for Medicine to Sir Macfarlane Burnet and Professor P. B. Medawar has caused great pleasure throughout Great Britain and the Commonwealth.[1] Their work, at once truly original and of fundamental importance to understanding the body's reactions in health and disease, has centred on problems of immunity and reaction to foreign substances introduced into the body. The concept of "acquired immunological tolerance," for the discovery of which they were awarded the prize, was first formulated in 1949 in Burnet and Fenner's prophetic monograph on *The Production of Antibodies*. It was here that there was put forward a theory of antibody formation which envisaged, and indeed necessitated, that the body should be able to distinguish clearly between its own tissue substances, such as structural proteins and cell enzymes, and substances of extraneous origin entering the body either by a natural process (as in bacterial infection) or by human action (as in the transfusion of red blood cells belonging to the wrong group or the grafting of another person's skin). Clearly, the argument went, the body is able to dispose of unwanted cells or materials in two distinct ways: *foreign* substances are eliminated as the result of antibody formation, whereas the body's own effete cells or damaged constituents are removed without the intervention of antibodies. Burnet and Fenner further developed this "self-marker" theory by suggesting that the time at which the capacity for recognition was stamped upon the body must be during embryonic life or soon after —that is, at a time when the body had not yet acquired the art of manufacturing antibodies. In other words, those cells which in the adult constituted the antibody-forming apparatus would learn to regard all substances present in the embryo as "self" and would fail to acquire the mechanism for forming antibodies against these, and only these, substances.

This theory led to several predictions, by far the most important of which was the idea that, if substances which would be antigenic to an adult were injected during embryonic life, they should inhibit the development of an antibody response. To show persuasively that this prediction was more than idle speculation Burnet and Fenner pointed to the remarkable work of R. D. Owen, who had shown some years previously that fraternal (two-egg) twins in cattle possessed not only their own red blood cells but also red cells which could have been obtained only from their corresponding twins during embryonic life. The fact that cattle fraternal twins almost invariably undergo vascular anastomosis in utero had suggested to Owen a satisfactory physical basis for the exchange of embryonic red cells and their precursors.

Meanwhile Medawar, in a series of classic investigations, had demonstrated that skin grafts transplanted from one individual to another belonging to the same species ("homografts") are destroyed as the consequence of an actively acquired immune response. Quite independently he and his colleagues then made a discovery which provided a dramatic link between Burnet's theory and Owen's experimental finding—the discovery that, quite against the rules of tissue transplantation, cattle fraternal twins accepted skin grafts exchanged between them although they reacted with unabated vigour against skin grafts from unrelated donors and even from their parents or non-twin sibs. Evidently the exchange of embryonic cells had resulted not only in the survival of these cells and their descendants but had also rendered the hosts impotent to respond to the donors' skin. The embryonic cells appeared to have established in their hosts a state of "actively acquired tolerance" embracing all the donor's tissue antigens.

It was at this stage that Medawar, together with R. E. Billingham and L. Brent, initiated a series of brilliant experiments designed to test and illuminate Burnet's theory. Using highly inbred strains of mice, they injected embryos with genetically foreign living cells. Their preliminary findings, published in 1953, showed that mice so injected frequently failed to react against skin grafts transplanted later in life. The situation occurring naturally in cattle twins had been reproduced in the laboratory and was now open to experimental analysis. The phenomenon of immunological tolerance had been put on the map. In the meantime, working against an entirely different conceptual background, M. Hašek in Prague had demonstrated essentially the same phenomenon by the artificial parabiosis of chick embryos—a very direct experimental reproduction of what occurs in the natural life of twin cattle.

Immunological tolerance was shown to be specific in the sense that it applied only to the cell donor's tissues and not to the tissues of genetically very different mouse strains; it was shown to be due to a

[1] See p. 1306 for biographical notes.
[1] Burnet, Sir M., *Brit. med. J.*, 1959, 2, 645, 720.

genuine failure of the antibody-forming cells to produce the relevant antibodies; and its induction was shown to be dependent upon the introduction of the antigenic material, in the form of living cells, either during embryonic life or very soon after birth. Soon other workers in many parts of the world confirmed these findings, and, by investigating this new phenomenon in different species and with a variety of antigens—from tumour cells to soluble heterologous proteins such as bovine serum albumin—revealed its widespread character. A new cornerstone for any comprehensive theory of the formation of antibody had been laid, and appropriately enough it was Burnet who recently put forward a new theory, his "clonal selection" theory described in his Croonian lectures last year,[2] which fully encompasses immunological tolerance. Moreover, though it may eventually be proved wrong, it has already stimulated new and critical experiments on this fundamental biological problem.

What of the medical implications? The techniques of immunological tolerance cannot, in their present form, be applied to human beings. Their most important implication is that the immunological obstacles which stand in the way of the grafting of foreign tissue are not as insurmountable as they had for many years seemed to be. The concept of immunological tolerance is also helping towards a better understanding of a number of diseases which are now being recognized as being due to the formation of auto-antibodies—antibodies produced by an individual against some of the constituents of his own body. The study of auto-immunity has received a tremendous stimulus as a result of the work of Medawar and Burnet and their colleagues, for immunological tolerance not only helps to explain why it is that the body does not normally react against its own tissue substances but also throws a light on the problem of why it sometimes does. Finally, it may be said that workers in the fields of radiation biology and cancer research have been much stimulated by both the ideas and the techniques of immunological tolerance.

THE MENTAL HEALTH ACT

The coming into effect next week of the main provisions of the Mental Health Act of 1959 is another milestone in the development of Britain's mental health services. The Act, like the report[1] of the Royal Commission upon which it is based, is in the main a reflection of that development, not its cause, for the remarkable progress made in the treatment of mental illness has had far-reaching effects. Psychiatry has taken its place in the main stream of medicine, and mental hospitals have become more actively therapeutic in aim, and are no longer being used mainly as places where the mentally disturbed and socially unacceptable can be kept in custody out of society's way. People are coming to realize that mental disorder is in fact an illness, that it is amenable to medical treatment, and that most of those who go into mental hospitals are soon well enough to be discharged. In fact, over 80% of patients newly admitted are discharged within six months and over 90% within two years. This has led to a much more tolerant public attitude towards mental disorder, and to an increasing readiness among those who are mentally ill voluntarily to seek the psychiatric treatment they need at an early stage. These changing attitudes have had two important consequences.

The first is the decline in the use of compulsory powers. Last year only 12% of admissions to mental hospitals were compulsory, compared with nearly 40% ten years ago; and only just over 15% of admissions to mental deficiency hospitals were under the provisions of the Mental Deficiency Acts, compared with virtually 100% only five years ago. The second development is the increasing effort being made to care for the mentally ill outside hospital wherever possible, leaving hospital beds for those who really need them. This desirable change depends for its success upon the continuing willingness of society to tolerate the mentally disordered in its midst, and therefore upon the ability of the mental health services to meet the demands that will be made upon them.

When the Act is examined against this background, it is not entirely surprising to find that for practical purposes, and so far as services are concerned, it makes no changes and confers no new powers or duties: all it does is to clarify the powers of local health authorities in certain respects. The drive to strengthen the community services is not dependent on it, and the statutory powers being used have been in existence since 1948. Why, then, is the Act important? First and foremost because it gives unequivocal recognition to the new position of psychiatry. It assumes as its starting point that psychiatry is like any other part of medicine and that mental health services are an integral part of the health services generally; that the object of psychiatric care is the treatment of the patient; that treatment for mental disorder ought to be available

[1] See *Brit. med. J.*, 1957, 1, 1349 and 1355.
[2] "The Mental Health Act, 1959. A Practitioners' Guide." By a Special Correspondent. *Brit. med. J.*, 1959, 2, 1478. Obtainable as a pamphlet from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1. Price 6d. net

in the same way as treatment for any other illness, without formality; and that the psychiatric services are as well able to keep their house in order as any other part of the health services.

Thus the Act repeals the old legislative framework in its entirety; the provisions for the designation of hospitals, with all the inflexibility they produced, disappear altogether, and the old code for providing compulsory care and treatment is replaced by a new, simplified one, applying to all types of mental disorder. The main changes affecting the work of medical practitioners were outlined in a special article published in this journal last year and since reprinted in pamphlet form.[2] The compulsory provisions form a major part of the Act in terms of bulk; but their relative importance is not nearly so great as this might seem to suggest, for the whole philosophy of the Act is that care and treatment will normally be obtained informally. The Act also does away with the previous arrangements under which a number of functions were reserved to the Board of Control as the central authority. Many of those functions are now transferred to individual doctors, hospital authorities, and local authorities. Special arrangements for central inspection are brought to an end, and the mental health services come on to the same footing as other parts of the National Health Service. The Act thus gives the clearest possible recognition to the fact that the psychiatric services have come of age.

One consequence of the Act is the disappearance of the Board of Control. The work done by the Board over the years deserves all the tributes that will certainly now be paid at its demise. It was under the supervision of members of the Board that the mental health services were built up (from almost nothing in the case of mental deficiency) to the level reached in 1948. They fostered all the developments which have made the Mental Health Act possible, and can take their leave knowing that their abolition, which they themselves proposed, is possible only because their work has been successfully completed. They will be missed by many not only for the service they gave but also because as whipping-boy they took responsibility for all that went wrong.

What of the future? Changes are certainly not at an end. On the hospital side, continued progress in the treatment of mental illness can be expected, more psychiatric units will be established at general hospitals, and out-patient services will be extended. The number of patients with chronic illness in mental hospitals should progressively decline, and this will lead to a reduction in the total hospital population. But it is to be hoped that the main emphasis will be placed on the development of "community" services for both the subnormal and the mentally ill. Here the family doctor, already playing an important part, has much to contribute. Better education in psychiatry in the undergraduate years and refresher courses afterwards will help the general practitioner of the future. The services provided by the local health authorities will have to be greatly extended. This will take time, but progress will largely depend on the amount of money available for new buildings and on the efforts made to recruit and train the necessary staff. The task is an urgent one, since upon the adequacy of these services may depend the degree of tolerance and kindliness shown by society to the mentally disordered. But if all those concerned show a sufficient sense of urgency in translating fully into reality the general principles underlying the Mental Health Act, then the future for the mental health services is full of hope.

LONDON'S LOCAL GOVERNMENT

After just under three years' hard labour the Royal Commission on Local Government in Greater London has produced a report,[1] and it is unanimous. The members spent 70 days examining witnesses, during which they asked 15,949 questions, and 88 days in visiting local authorities. Though few will agree with every recommendation in the report and many will object to one or more of the details, the commissioners have produced a report which reads well and, in broad outline, is convincing. It is the first comprehensive report on London government since 1834, though in the meantime four Royal Commissions have tackled some aspect of the subject; it is an indication of the feelings aroused and the complexities of the matter that no action was taken to implement their findings. The recommendations of the present Commission, under the chairmanship of Sir Edwin S. Herbert, a distinguished lawyer, deserve a better fate. But, as a comment on the evidence and a foretaste of what is to come, the commissioners say that a "parochial outlook is still very much alive."

Local government is "the machinery by which the people govern themselves." Greater London, as dealt with in the remit, has a population of 8,714,000, one-fifth of that of England and with a rateable value which is one-third of that of the whole country. The thesis is developed in the report of the Royal Commission that local government must be dealt with as a whole, which brings to the mind of the medical reader the discussions in our own field about regarding a sick person as a whole and not simply as one in whom a particular organ does not function normally. Just as all the organs of the body are interrelated, so inefficiency in one department of local government has reactions on the whole. As might be expected, considerations relating to town

[1] *Report of the Royal Commission on Local Government in Greater London, 1957-1960.* H.M.S.O., London. Price 28s. net.

and country planning, housing, and traffic occupy much space in the report and dominate the picture, though education, the personal health, welfare, and children's services, and environmental health services are by no means neglected. In fact, education is stated to be "the most important of local authority functions" and receives full treatment.

The chapter on the personal health, welfare, and children's services is the one of most interest to medical readers. It describes the overlaps of these three local services with each other and with the functions of other authorities. It emphasizes the importance of the local officers working as a team in the same building. From the fact that they deal with people in their homes the responsible officials must be readily accessible, and the report draws the conclusion that for this type of service the "smallest practicable local authority is desirable." It considers that between 100,000 and about 200,000 is the right population for efficient administration, and goes on to say: "The vital objective is to achieve the domiciliary team with the family doctor as its clinical leader and one local authority officer as its organizer." On the other hand, it is as well to remember that the results of organizational changes are incapable of being subjected, except in the broadest possible way, to objective tests of efficiency, and in the final result all that issues forth about the optimum size of a local authority for these purposes is an opinion. Stress is laid on the value of welfare work (mainly services for the old and disabled) being a responsibility of the medical officer of health.

The commissioners conclude that the present structure of local government in Greater London is inadequate to deal with many of the major problems. They discuss various suggestions which have been put forward and finally come down in favour of one of their own devising. It is that there should be a council for the whole of Greater London to deal with functions for which a large area is essential, such as traffic: it would also be the education authority (though not for the school health service), the planning authority, and be responsible for the ambulance service (possibly as a section of the fire service) and for refuse disposal but not refuse collection.

The commissioners' opinions about the need for the personal services to be administered by as small an authority as possible lead them inevitably to the conclusion that Greater London should be divided into a number of Greater London boroughs—not as second-tier authorities but independent for the functions they administer. This will require the amalgamation of some existing authorities and a reduction in their total number from 95 to about 52. The London and Middlesex County Councils will disappear entirely, and Essex, Hertfordshire, Kent, and Surrey will be shorn of their metropolitan districts.

These drastic changes will need legislation, and, at best, cannot be implemented without prolonged discussion and controversy about details. It may take years, and in the meantime the authorities doomed to disappear or to have their activities curtailed cannot be expected to initiate new developments in their services. Thus stagnation may result. Many professional organizations will be kept busy in safeguarding the interests of their members. The effects on staff of such wide changes in a large part of the country are not mentioned in the report. It does, however, say that any settlement reached now should last for at least a generation: this comment is in relation to "the morale of local government," presumably at member level, but it applies to officers as well. It is to be hoped, therefore, that after all the bargaining there will be a stable structure which might at least be expected to last as long as an ordinary lease of land, which is 99 years. No authority can attract good staff when there is a risk that every few years the doctor, nurse, or other professional worker may see his office abolished, with or without compensation, or that he may have to change his employer and his status.

These proposals are unlikely to help the integration of the three limbs of the National Health Service. Instead of five county councils and three county boroughs with whom the metropolitan regional hospital boards and executive councils have to co-operate there will, if the proposals are adopted, be 52 independent authorities administering the midwifery and other domiciliary services. On the other hand, integration at the level of hospital management committees may be easier.

FRINGE MEDICINE

Sir James Paget about 80 years ago said to his colleagues at Bart's that if they did not learn how to manipulate their patients they would lose them to the bone-setters. Many years later the bone-setter Sir Herbert Barker showed by the great success of his life and work that the medical profession had still not learnt Sir James Paget's lesson. A profession which struck the unfortunate Dr. Axham off the *Register* for giving anaesthetics to Barker's patients ended up by almost canonizing Barker at a meeting held in his honour by the British Orthopaedic Association in 1936. The registered medical practitioner will always tend to distrust those who practise what this week's *Spectator* calls "fringe medicine." Ever since doctors have been officially registered—that is since 1858—those in charge of medical education in this country have rightly looked upon it as their task to produce a "safe doctor" for the general public. Such a training is bound to have its limitations. The teacher is bound to be dogmatic—and in medicine unfortunately finds it easy to be so. If

the "safe doctor" departs from accepted teaching, then, particularly in these litigious days, he is open to savage financial penalty if something goes wrong.

Yet medical teachers and medical practitioners have seen so much harm to patients treated by unqualified healers of one sort and another, and have seen so much charlatanry among them, that they best serve their patients by being sceptical about claims of healers who, apart from being unqualified, differ in one important respect from doctors—they never seem to publish their failures.

We do not know whether the *Spectator* is right in believing that "the public is flocking in increasing numbers to practitioners outside the Health Service offering treatments which orthodox medicine affects to distrust or despise." It is probably impossible to make any comparison between what happens now and what happened before 1948 in this respect. The unqualified healer has always had his own peculiar attraction for certain types of people, particularly for the rich with time on their hands and money to spend and for the egg-head obsessively interested in himself. The *Spectator* may be right when it states: "Obviously nobody, *except a crank*, would pay for treatment if he could get as good on the N.H.S. for nothing." (Our italics.) But there never has been in the whole history of medicine a shortage of cranks in any society enjoying the alleged benefits of civilization.

Nevertheless we can be grateful to the *Spectator* for inviting Mr. Geoffrey Murray of the now deceased *News Chronicle* to write his survey in the current week's issue on "Fringe Medicine." He includes homoeopaths, chiropodists, osteopaths and chiropractors, herbalists, the practitioners of naturopathy, psychotherapists, faith healers, and the self-treaters. Some of these are properly recognized by the medical profession and are not on the fringe. We may have something to learn from the others. If high-powered business executives eat and drink too much, then they will probably benefit much more by going to an establishment where they pay large sums of money in order to drink nothing but orange juice for a week or two, than by attending an earnest conference held by the Chest and Heart Association.

Whatever else Mr. Murray's interesting survey may prove, it rubs home the point that people are above all things suggestible. The writers of books on motivational research and the hidden persuaders have demonstrated in an unpleasantly compelling way just how this suggestibility of the human animal can be exploited. It has always been, and will always be, exploited in matters of health and disease. But this does not mean that the painfully educated registered practitioner of medicine has not something to learn from the unorthodox healer. There is, after all, no "orthodoxy" in medicine. It may well be, too, if the *Spectator* is right in its surmise, that people are going to unorthodox healers because of their suspicion that they may not get something "as good on the N.H.S. for nothing." Perhaps the *Spectator* will let us have a symposium on the theraupeutic value of paying at least something, however little, for the ministrations of the healer.

SAFETY OF ELECTRIC BLANKETS

"'Tis very warm weather when one's in bed," said Swift. The electric blankets now used on an increasing scale to preserve this illusion are distinctly more dangerous than the warming pans or hot-water bottles favoured before science took a hand. Electric blankets were blamed for more than 2,600 fires in a recent year and have caused 20 deaths since the beginning of 1958.[1] The hazards responsible for these accidents have been studied by the Fire Protection Association and by the Consumers' Association.[2] Their conclusions are disturbing.

An electric blanket is basically a length of high-resistance wire embedded in a fabric cover and joined to the electric supply. As in every kind of electrical apparatus, the insulation protecting the live conductors is bound to deteriorate with age and may eventually fail. The danger of electric shock, though less serious in a bedroom than in the moist atmosphere of a bathroom or greenhouse, is still evident and can be minimized only by careful attention to recognized principles of design and construction. Nearly all of the British electric blankets tested by the Consumers' Association were satisfactory in this respect, even after treatment representing long periods of use. A low-voltage electric supply, obtained through a transformer, is an additional safeguard adopted by some manufacturers.

The risk of fire is less obvious but more important. An electric blanket of simple design will rise in temperature until the heat lost to the surroundings becomes equal to the energy input from the electric supply. If the blanket is folded, or overlaid with pillows and bedding (which are excellent insulators), it may reach a dangerously high temperature: 400 fires were caused in this way in 1956. Even if the blanket is not overheated, internal sparks (caused by a break in the element) or short circuits (caused by failure of insulation between adjoining sections of the element) may give the same result. One way to prevent a dangerous rise in temperature is to fit thermostats at several points in the blanket, so that overheating will switch off the electric supply. A further measure of protection is gained by limiting the loading (in watts per square foot of blanket area) to a level which will be reasonably safe even if the thermostats fail.

Standards for the design, construction, and performance of electric blankets have been formulated in Britain, the United States, and New Zealand. The British requirements are the least exacting; none of the blankets tested by the Consumers' Association would have satisfied the United States or New Zealand recommendations. Only seven of the 13 samples examined were in conformity with the current British Standard Specification, though three of the six unsatisfactory models bore the "kitemark." Further investigation and guidance to manufacturers is clearly desirable. Meanwhile a few simple rules can be suggested for the protection of users. An electric blanket should never be folded or creased, should not

[1] Statement by the Fire Protection Association, October 11, 1960.
[2] *Which?* 1960, October, p. 215.

be used when wet, and should not be covered with pillows or heavy bedding while connected to the electric supply. Most of the fatalities so far recorded have been among people lying on electric blankets with the current still switched on. This practice, though very common, should be discouraged by all available means.

SUICIDE AS A CRIME

A year ago a letter from the Home Office to the Criminal Law Revision Committee[1] stated that the Home Secretary was "considering whether legislation should be introduced to provide that suicide and attempted suicide should no longer be criminal offences." The letter pointed out that abolition of the offence of suicide would involve consequential amendments of the criminal law to deal with offences which would cease to be murder if suicide ceased to be self-murder. "The actions of one who encourages or assists suicide may range widely in moral culpability, and it seems proper that any such consequential amendments should be framed in such a way as to enable the courts, in assessing penalty, to take account of these distinctions." Consequently, the Home Secretary asked the Criminal Law Revision Committee to consider how the law should be amended if suicide and attempted suicide ceased to be crimes. But the Committee was to act on the assumption that it should continue to be an offence for a person to incite or assist another to kill or attempt to kill himself. The Committee's report,[2] issued last week, is welcome as a contribution to the more humane and effective treatment of those unfortunates who attempt to commit suicide. It relates in the main only to England and Wales, because the law is different in Scotland and Northern Ireland.

At present suicide is regarded in England and Wales as self-murder; consequently anyone who attempts suicide is committing a common-law misdemeanour. In recent years legal proceedings have been taken against about 10% of the total number who are known to the police to have attempted suicide, and a small number of persons annually have been sent to prison for the crime. Statistics compiled by a Joint Committee of the B.M.A. and the Magistrates' Association[4] showed that during 1946–55 5,794 attempted suicides in England and Wales were brought to trial and 5,447 found guilty. Of these, 308 were imprisoned without option of a fine. However, in 1959 out of 4,980 cases of attempted suicide known to the police, proceedings were taken in 518 cases and none were sent to prison.[3] The Committee emphasizes that such people are "in a state of mental distress and unhappiness" and need "special sympathy and understanding." Nobody would dispute this nowadays, and there is no reason to suppose that public opinion in general differs from medical opinion or wishes for further delay in amendment of the law—indeed, rather the contrary.

The second important consequence of treating suicide as self-murder is that a person who "aids, abets, counsels or procures another to commit suicide is guilty of murder, though in the case of suicide pacts this may be reduced to manslaughter."[2] The Criminal Law Revision Committee recommends a change here to follow on the abolition of suicide as a criminal offence. This is that a person found guilty of aiding another to attempt or commit suicide shall be liable to a maximum sentence of imprisonment for 14 years (instead of life imprisonment for murder). The report concludes with a Draft Suicide Bill, and it seems likely that this will soon be introduced into Parliament. The first clause abrogates the law whereby it is a crime for a person to commit suicide, and the second defines the criminal liability of a person who aids another to attempt or commit suicide.

[1] Members: Lord Justice Sellers (chairman), Lord Justice Donovan, Mr. Justice Edmund Davies, Mr. Justice Marshall, Professor D. R. Seaborne Davies, Mr. Mervyn Griffith-Jones, Sir Anthony Hawke, Mr. J. R. T. Jones, Mr. F. H. Lawton, Q.C., Sir Theobald Mathew, Mr. Frank Milton, Mr. A. C. Prothero, Mr. James Whiteside, Dr. Glanville Ll. Williams, Brigadier A. C. C. Willway, Mr. G. V. Hart (secretary), Mr. P. N. S. Farrell (assistant secretary).

[2] Criminal Law Revision Committee: Second Report (Suicide). Cmnd. 1187. H.M.S.O. (9d.).

[3] *Criminal Statistics, England and Wales*, 1959, Home Office, Cmnd. 1100. H.M.S.O.

[4] *Brit. med. J.*, 1958, 1, 1233.

ELDERLY DRIVERS

At the annual meeting of the Magistrates' Association last week Dr. J. F. Fisher raised the question of the standards set, or not set, by insurance companies when they requested an elderly driver to provide a medical certificate to state that he was fit to drive.[1] On inquiry, Dr. Fisher had found that the insurance companies "left it to the doctor." This vagueness is unsatisfactory,[2] and in 1959 the Representative Body of the B.M.A. referred a motion to Council recommending that the circumstances under which a medical certificate of fitness to drive are required should be legally defined and that there should be a right of appeal to an independently appointed referee.[3] Since then the Private Practice Committee has prepared a draft medical report form at the request of the Accident Offices Association[4] and there have been consultations with officials of the Ministry of Transport about the fitness and ability of the elderly to drive cars.[5]

When the Minister of Transport was asked at the meeting of the Magistrates' Association to comment on the standards of fitness that should be required, he is reported to have said, "I should have thought the only test of fitness to drive was a driving test."[1] He added that the insurance companies had been asked to let the Ministry of Transport inspect insurance records. The object of this would be to provide statistical information (not individual details) about accident proneness in relation to age groups. If the records reveal that elderly drivers are any more dangerous to themselves and others than younger people, then there is all the more need for agreement on the form of medical examination which the elderly may be required to undergo. But what if the records show that the young are more dangerous than the old?

The next session of the General Medical Council will open on Tuesday, November 22, at 2.15 p.m., when the President, Sir David Campbell, will take the chair and deliver an address.

[1] *The Times*, October 22, 1960.
[2] Stratford, M., *Brit. med. J.*, 1959, 1, 442.
[3] *Supplement*, ibid., 1960, 1, 139.
[4] *Supplement*, ibid., 1959, 2, 206.
[5] *Supplement*, ibid., 1960, 1, 198.

FIRST B.M.A. LECTURE-DISCUSSION

DR. PAUL WOOD ON SELECTION OF CASES FOR CARDIAC SURGERY

An audience of nearly 200 was present for the first of a new series of B.M.A. lecture-discussions at B.M.A. House on Thursday, October 20. The lecturer was Dr. PAUL WOOD, director of the Institute of Cardiology, and he was speaking on "The Selection of Cases for Cardiac Surgery." In introducing the speaker, the chairman, Sir ARTHUR THOMSON, said the occasion marked a new venture on the part of the British Medical Association. The Council had decided to sponsor a series of lectures by those working on the fringes of advancing knowledge. The lectures were to be delivered at B.M.A. House in order to signalize the Association's profound interest in the progress of Medicine.

Coarctation of the Aorta

Dr. PAUL WOOD explained that his lecture was based on 2,000 cases of congenital heart disease, 85% of which were operable, and approximately one-third of which had in fact been operated on. He began with congenital aortic stenosis. These cases were recognized by the murmur and possibly by symptoms consisting of effort syncope or effort angina. No patient suffering from congenital aortic stenosis died abruptly unless the condition was severe. Those with syncope or angina were severe cases. The pulse in congenital aortic stenosis was abrupt and sharp, often lacking the features of the pulse in rheumatic aortic stenosis. To avoid mistakes, it was essential to feel both brachial pulses. Turning next to coarctation of the aorta, Dr. Wood said there were 182 cases in his series, most of which had been operated on. Coarctation could cause heart failure in infancy, but was not usually associated with symptoms in childhood. In adult life the hazards of infective endocarditis and local complications began to appear. If the patient survived to the age of 60, left ventricular failure and coronary artery disease were likely to become troublesome features. If hypertension was of moderate severity in childhood, it was likely to be severe in adult life; accelerated hypertension did not occur because the renal vessels were protected. The degree of coarctation could be gauged from the femoral pulse. Angiography delineated the anatomy but was not required for diagnosis, which was made clinically. Resection of the coarctation, which was indicated in moderate and severe cases, was not without some risk, and severe hypertension might occur after operation, perhaps as a result of increased pressure in unprepared renal vessels. Original results of operation were excellent in 60%, good in 20%, fair in 4%, poor in 4%, and fatal in 12%. In uncomplicated cases the mortality was under 10%.

Septal Defects

Atrial septal defect was not recognized in infancy unless of the ostium primum type. In the ostium secundum variety symptoms usually appeared in the second or third decade, and by the age of 50 years atrial fibrillation had developed in about half the patients. This was usually catastrophic, leading rapidly to severe heart failure. Most patients with large secundum defects died by the age of 60, and had severe symptoms at the age of 50 to 55. In the small group with severe obstructive pulmonary hypertension and reversal of the shunt (the Eisenmenger syndrome), death occurred earlier. The severity of the condition could be gauged by the physical signs at the bedside: if the second heart sound, the cardiogram, and the heart size were normal, the case was mild and the ratio of pulmonary to systemic blood flow less than 2:1. If the second sound was fixed, and did not widen on inspiration, the cardiogram showed an rSr' pattern, and the heart was enlarged, the flow ratio was greater than 2:1. Operation was not indicated in the mildly affected patients, who might reach the age of 80 and made up about 5% of all cases. Although the mortality of closure was nil in expert hands, the morbidity was far from negligible, being around 18%, and consisting of such complications as cerebral embolism, dementia from cerebral damage due to too prolonged circulatory arrest under hypothermia, recurrent pericarditis, staphylococcal chondritis, and persistent atrial flutter.

The natural history of ventricular septal defect was not fully known. Few cases were seen in adult life, and scarcely any defects were noted as incidental findings at necropsy in middle-aged or elderly people. What happened to patients with ventricular septal defects in later life was a mystery. In view of this lack of knowledge, mild cases with small defects, a pulmonary:systemic flow ratio of less than 2:1, and normal pulmonary vascular resistance should not be operated upon when diagnosed in childhood, for such patients were symptomless and enjoyed a normal tolerance for all forms of exertion. Severe cases, with a flow ratio of 3:1 or more and pulmonary hypertension, required operation as soon as possible after diagnosis, for symptoms were usually appreciable. Operation on moderately severe cases with flow ratios of between 2:1 and 3:1 should be deferred until the risks were less than 5%. When the Eisenmenger reaction had occurred and the pulmonary vascular resistance was at systemic level and the shunt negligible, operation was completely contraindicated.

Patent Ductus and Pulmonary Stenosis

Patent ductus arteriosus not infrequently caused heart failure in infancy, when closure was often life-saving. Some infants exhibited the Eisenmenger reaction, and operation was too late if delayed past the first year of life. With small ducts the life expectancy was normal apart from the hazard of infective endocarditis, which carried a 20% mortality. Since the mortality of surgical closure of the uncomplicated small patent ductus was 0.5% in skilled hands, operation should be advised in all such cases. Diagnosis could be made with certainty at the bedside and should not be doubted because of anomalous catheterization results. However, an apparent ductus murmur could arise from other causes, such as an aortic pulmonary window, and if at thoracotomy the ductus was found to be closed search must be made for the site of the fistula elsewhere. A large patent ductus in adults might be overlooked, atrial fibrillation could occur, and the signs be misinterpreted as those of rheumatic heart disease: diagnosis was vital, for the results of ligation of the ductus could be dramatically beneficial.

In pulmonary stenosis with closed ventricular septum the natural history depended upon the severity, and there was a striking difference between mild and severe cases. In the latter, the mortality rate increased steadily with age and early death was inevitable unless surgical relief was available. In such patients, especially those with reversed interatrial shunt, the operative mortality was high (10–15%), but must be accepted without question in view of the serious medical prognosis. Mild and moderately severe cases were quite different, and symptoms did not progress. When the right ventricular systolic pressure was less than 75 mm. Hg, patients could have a full effort tolerance and be free of symptoms even at the age of 65 years. There was no point in operating to reduce the right ventricular pressure from 60 to 25 mm. Hg, for the right ventricle was quite capable of coping with that level of pressure. Moreover, the surgical morbidity was appreciable.

The most satisfactory surgical management of the tetralogy of Fallot had not yet been achieved. Full correction with closure of the defect and resection of the pulmonary stenosis could be dramatically effective, but the operation was difficult, and the overall results still disappointing, the mortality rate being high even in the best hands. In very severe cases with extreme cyanosis and an inadequate outflow tract of the right ventricle full correction might be impossible. Pulmonary valvotomy by the method of Brock

often gave satisfactory results with a mortality of only 5%. However, operation should be delayed in less severe cases until the results of full correction had improved, unless there were syncopal attacks, which were an urgent indication for some form of surgical relief, though not necessarily complete correction.

Rheumatic Heart Disease

Turning to rheumatic heart disease, Dr. Wood discussed the natural history of mitral stenosis, stressing the long latent period before the onset of symptoms, and the considerable variation among patients. The results of operation could be dramatic, and the mortality in uncomplicated cases was 1–3%. The surgical morbidity was not inconsiderable, consisting of recurrent pericarditis, the after-effects of systemic embolism if this occurred during valvotomy, established atrial fibrillation, and the production of mitral incompetence which could be catastrophic. Finally, restenosis of the valvotomy was an unquestioned possibility, occurring in 1–2% of patients each year and probably increasing in frequency. The latent period before the development of restenosis varied, but could be as short as 12 days. The probability of restenosis apparently increased with each valvotomy. For these reasons premature mitral valvotomy was not advisable, and patients should not be submitted to operation until the degree of obstruction to the valve was interfering with life.

In a small group of patients heart failure and atrial fibrillation appeared to be related to myocardial disorder rather than to severe valvular disease, either stenosis or incompetence. Such patients had signs of mild stenosis with a short mid-diastolic murmur and late opening snap. The left atrial pressure was near normal at rest and modestly elevated in exercise. Operation did not help this type of disease. Valvular calcification was often an important sign of severe valvular damage and could be suspected clinically by poor quality of the first heart sound and lack of opening snap. Possibly such valves were better operated upon under direct vision with the bypass. Patients with severe pulmonary hypertension and high pulmonary vascular resistance due to mitral obstruction always required early valvotomy, for the medical mortality was 100%. Unfortunately the surgical mortality was high, in the region of 20%, and pulmonary thrombo-embolism a real risk, so that the operation should be performed under anticoagulant cover.

Questions from the Audience

Answering questions put by the audience, Dr. Wood said that a stenosed aortic valve of rheumatic origin was usually calcified (in adults), and the difficulty was to select the severe cases for operation before the critical stage had been passed. The medical mortality of severe aortic stenosis was very great. Transventricular valvotomy gave better results in some surgical hands than others, the mortality varying from 15 to 50%. The operation was not really satisfactory, and attention naturally turned to open operation with the bypass. Here the ischaemic myocardium often led to difficulties, and possibly the combination of perfusion with deep hypothermia offered the best prospects. In the worst cases a quick transventricular valvotomy might be the best approach; in the less severe, deep hypothermia should be considered.

Open repair of mitral incompetence gave very indifferent results, but some appeared to be good. In Britain, Wooler and his colleagues had described a special type of mitral incompetence due to a shrivelled posterior mitral valve cusp with a mobile aortic cusp. This situation could be detected clinically by the association of the signs of mitral incompetence with a loud opening snap, and the valve could be repaired by a prosthesis in the posterior cusp.

Asked about the place of surgery for angina and coronary-artery disease, Dr. Wood said he regarded the condition as basically medical rather than surgical. Medical treatment certainly had something to offer in the form of substances which inhibited cholesterol synthesis and in the use of anticoagulant drugs.

PSYCHOPATHOLOGY AND TREATMENT OF SEXUAL DEVIATION

[From a Special Correspondent]

Sexual deviation was the subject of a two-day conference held in London on October 11 and 12 and sponsored by the Portman Clinic as a contribution to Mental Health Year.

Opening the conference, Mr. Kenneth Robinson, M.P., said that the laws pertaining to sexual behaviour in Britain were more illiberal and oppressive than in any other civilized community. This contrasted with the liberality of the law in general. He did not think that this state of affairs reflected an exaggerated puritanism in the population as a whole. The answer, he thought, must be sought in the law-making body itself, the House of Commons. The recent debates in the House on the Wolfenden Report had demonstrated a degree of timidity, intolerance,, and prejudice proportionately far in excess of that existing in the population generally, at least in so far as this could be judged by the attitude of the Churches, general press comment, and such straw votes as had been carried out. The objections to a change in the law were irrational and were not addressed to the known facts. No further research was required to show the need for change.

Aetiology and Treatment

Dr. D. Stafford-Clark said that in the aetiology of sexual deviation differing degrees of emphasis had been laid on genetic, constitutional, conditioning, and psychopathological factors. The relation of physiological and genetic variants to sexual deviation was not clearly defined. Twin studies had provided support for the genetic basis of at least some proportion of homosexuality. It seemed possible also that in both sexes androgens might decide the vigour of the sexual impulse and oestrogens its direction, although the evidence for such endocrinological basis was admittedly slender. Recently it had been claimed in some quarters that conditioning could cure all, but he doubted its value and in any event regarded it as an undesirable form of treatment. In all cases psychotherapy was invaluable and a necessary preliminary to any other approach. In treatment one must have an abiding respect for the dignity of the individual and a clear conception of one's own ethical position. Except in the case of a true hermaphrodite he would never recommend a sex-change operation. It had to be understood also that drugs such as oestrogens and androgens were purely palliative. With psychotherapy prognosis was best with the adolescent group and worst with the well-developed constitutional type. The first essential was that the patient himself should seek to be treated.

Psychopathology

Outlining current psycho-analytic thought on the psychopathology of sexual deviation, Dr. W. H. Gillespie said that in perversions there was a persistence into adult life of elements of infantile sexuality at the expense of adult genitality. There had been a failure in the normal transformations occurring at puberty. Neither had these conflicts been dealt with by the conventional defence mechanisms leading to neurosis, so that the infantile sexual elements, instead of being converted into neurotic symptoms, seemed to persist in unmodified form. Later work had shown, however, that the overt perversion represented only the conscious part of a much bigger unconscious system and came into being through the preservation in consciousness of a specially suitable piece of infantile experience on to which the rest of the infantile sexual pleasure was displaced. The ego had employed the solution of "division," whereby

it had repressed the greater part of infantile sexuality at the expense of sanctioning the smaller part, which, as it were, it took as ally in maintaining repression of the rest. The part which was allowed conscious expression might be chosen because of its inherent strength (the result of innate or developmental factors), which made it more difficult to repress. But equally it might be determined by the ego's estimate of what was acceptable or at least not repugnant to the superego—that is, the internalized parental imagos. In the final analysis, it was fear, often an intense castration anxiety, which had driven the ego to employ these defence manœuvres so characteristic of perversion.

Observations on Animals

Professor N. Tinbergen referred to work on animal observations, illustrating this with film. Premating "courtship displays" in some territorial species were found to be similar to hostile displays and often alternated with overt attacks and overt escapes. But they also contained another category of movement, an "appeasement" posture which had a hostility-inhibiting effect on the other individual. These postures were aroused by the simultaneous arousal of escape and either attack or a more general tendency to stay. It was such postures which in pair formation seemed to allow sexual behaviour to dominate over hostile behaviour.

The Male Homosexual

Dr. L. H. Rubinstein spoke of the problem of identifications in male homosexuals. The homosexual of predominantly active type had to maintain a precarious balance between conflicting identifications, with, on the one hand, the active father-mother image, and, on the other, the passive child. The latter was bound to remain the stronger in most cases. In the passive homosexual, childish dependency and identification with the feminine receptive mother, reinforced by a negative Oedipus complex, pointed in one and the same direction. He could also feel identified with his partner, the stronger man who often represented the active aspect of the mother as well as the father. However, he obtained direct gratification of his passive-infantile desires, whereas the active homosexual could do so only vicariously through identification.

Dr. W. Paterson Brown described the clinical treatment by psychotherapy of male homosexuals. He believed that unreasonable scepticism about the prospects with treatment had often contributed to its failure. The essence of treatment lay in the doctor–patient relationship and centred upon interpretation. The important instincts were jealous and aggressive as well as sexual. The best results were obtained with young intelligent subjects, preferably with no serious defect of appearance, health, or education.

Aggression

Dr. E. Glover, speaking of the role of aggression in sexual deviation, said that the perversions were in fact defences against an overcharge of unconscious aggression. In stressing their defensive aspects he did not wish to minimize the more positive instinctual factors—that is, the relative constitutional strength or weakness of the aggressive drives and of the components of infantile sexuality. Aetiology should embrace constitutional, predisposing (endopsychic), and precipitating factors (either immediate or summating). For any form of deviation one should seek to establish the combination of factors which lead to that end-result and to isolate the points at which the factor of aggression played a determining role. Excess of infantile aggression predisposed to perversion. In the perversions there had been a miscarriage of sublimation and he believed that aggression was responsible for such.

Exhibitionism

Dr. I. Rosen discussed the group treatment of exhibitionism and said that statistics and clinical experience showed it to be one of the commonest sexual deviations in Britain. Broadly speaking, exhibitionists tended to fall into one of two main groups, (*a*) the simple or regressive where the deviant behaviour followed upon some rather obvious social or sexual trauma or as an accompaniment to a mental or physical illness, and (*b*) the phobic-impulsive type with much more intense personality disturbance, often of amoral cast of mind and prone to other forms of character disorder and perversion, as well as to stealing. In this latter group, also, could be found well-developed phobic disorders of both hysterical and obsessional type. The preconditions and liability for the exhibitionist act existed in childhood, where desires and acts of exhibitionism were normal and later underwent repression. Age of subsequent onset of exposure was highly variable — usually in puberty. Commencement in later decades was usually the result of loss or frustration. The circumstances of the first exposure experiences tended to become conditional and an habitual pattern was set up. Where such specific conditions existed, each element of the situation must be worked through in therapy. Stilboestrol might banish all sexual fantasy, but this would return immediately on discontinuing the drug. Exhibitionists tolerated depression very badly and exposed themselves as a defence against it, while the tendency to react in this way was probably reinforced by constitutional disposition. The results of treatment by psychotherapy were gratifying; he himself had treated 14 adult patients of the phobic-impulsive type, and after varying lengths of treatment 13 appeared to have stopped exposing themselves. The results with a group of adolescents were also encouraging He felt that in all cases of exhibitionism referral to a psychiatrist was indicated.

Sexual Murderers

Dr. A. H. Williams, speaking of the psychopathology and treatment of sexual murderers, said that of all kinds of murderer it was the sexual type who had the tendency to repeat the same pattern of crime. He was less amenable to rehabilitative measures because he was not properly aware of his real motivation. Although the workings of the mind of the sexual murderer were to some extent understood, it was not possible to say why some people actually committed murder and others who appeared to be similarly predisposed did not do so. The murderous act was but the visible part of a much larger unconscious system, to the elucidation of which he believed much would be contributed by the application of Freud's theory of life and death instincts, especially as developed by Melanie Klein. Ideally such patients should have the benefit of full psycho-analysis.

Anthropological Studies

Dr. M. Carstairs discussed the significance of cultural variants in the field of sexual deviation. The normality of any sexual act must be judged in the context of the environment, both physical and social, in which it occurred. It was not always easy to define which behaviour was "natural" or biological and which was the product of human learning. Anthropological studies had shown considerable variations in cultural attitudes towards particular forms of sexual activity. Exhibitionism could only be properly understood if viewed in its social context—it was not nakedness as such but the deliberate flaunting of a social convention which constituted indecent exposure. By their restrictive and condemnatory attitudes to sexuality, many societies appeared to condition their young so that they failed to experience sexual satisfaction in adult life. The anthropological evidence on sexual deviation, save in the case of homosexuality, was incomplete. The evidence both from anthropology and also from comparative psychology supported the contention that all human beings were capable of learning to respond in homosexual relationships: this potentiality was realized in all the members of some societies but in only a few members of the others.

THE TRAINING OF A SURGEON

DISCUSSION AT INTERNATIONAL FEDERATION OF SURGICAL COLLEGES

The "rather haphazard" way in which graduates are selected for training as surgeons was the subject of comment by Professor DIGBY CHAMBERLAIN, Vice-President of the Royal College of Surgeons of England, at the London Meeting of the International Federation of Surgical Colleges, held at the Royal College of Surgeons from October 18 to 20.

Fellowship of the College, he said, did not mean that a man was a trained surgeon; it merely indicated that the trainee had passed two examinations. "We do not select trainees we consider likely to be competent surgeons. It might happen that a young graduate is encouraged to apply not because he is considered suitable for training but because there happens to be a vacancy at that moment and we want someone to fill it at junior level. Once appointed, he tends to get further appointments, and in this way he makes his way up the training ladder, sometimes with very happy results, but in other cases leaving him in difficulties when he sits his final examination or applies for a consultant post." The system, he said, seemed to work reasonably well, but they should perhaps look for some better method of selection. "We know what the F.R.C.S. means, and it is universally respected throughout the world. We see no point in changing it. The Fellowship should therefore be regarded as an intermediate test of knowledge and not as the hallmark of a fully trained and experienced surgeon."

The courses provided at the College, Professor Chamberlain continued, were in no sense cramming courses for an examination. They were designed to give instruction at a sufficiently high level for the candidate to have the sound knowledge of the basic sciences thought necessary if the surgeon was to be anything more than a mere technician. The courses for the primary examination were much in demand all over the world, and 22 nationalities were represented among the present students. The primary examination was also held in centres outside Britain; it had been held in Ceylon and the Sudan and it was probable that in 1962 it would be held in Pakistan. The courses for this would in future last for 24 weeks instead of 15 and would take place once a year instead of twice. The numbers attending would be increased from 60 to 90: there were usually about 300 applications. The new arrangement would ease the burden on the academic staff and enable them to devote more time to research.

Surgical instruction had not been given on a large scale in the College, because it was felt that most of this should be obtained in the practical appointments candidates held. But many candidates felt that they would benefit from a refresher course, and a surgical tutor had been appointed. The College was considering enlarging the department and appointing a director in charge of it. A professor of surgery might also be appointed, with his first duty in connexion with research work on fundamental surgical problems.

Mr. HAROLD EDWARDS said that a ladder-pattern of promotion to consultant rank had been developed in the National Health Service, and to side-step the ladder might put the aspirant to a consultant post at risk. Service for a time, particularly towards the latter part of the training, in one of the less-advanced countries in the Commonwealth could be of mutual advantage. Unfortunately, anyone choosing to do this was in some danger of losing his place on the promotion ladder.

Foreign Views

Speakers from the Continent indicated that, though the length of training was similar to that in England, there was no final examination. Professor F. LINDER (West Germany) said that the advantages of an examination were being discussed in Germany, because the majority of hospital appointments were made by committees on the basis of certificates and letters presented by applicants. "You can imagine how that works under the influence of democratic parties and religious groups," he said. But there were disadvantages to the examination system, too, and Switzerland had firmly rejected it. Another difference from the British system was that resident surgeons were appointed for longer periods—even for life—and the rotation was therefore less. "We are not so fortunate as the British, in that the surgeon is picked exclusively by the Royal College; in Germany a man who has applied unsuccessfully 20 or 30 times may join the strongest party in the city or marry the burgomaster's daughter, and then get the position."

Mr. H. OSMOND-CLARKE said it was depressing when highly trained specialists from this country and America were sent to under-developed countries without the facilities essential to their work. He had worked in a country as big as Europe in which there had not been one physiotherapist. He supported a plea made by a representative of the World Health Organization that special attention should be paid to the provision of these collaborative services, without which the surgeon could not apply his skill. We were living in the era of the high-velocity injury; the great killing injuries were those to the head and chest. A young surgeon could obtain his F.R.C.S. and still not be able to handle these emergencies. When an injured patient was admitted to one of the big hospitals there was no difficulty because there were many specialists present. A first-class abdominal surgeon could be obtained at once, for instance, to remove a spleen. But even in Britain there were remote areas where such specialists were not available. "We must see to it that our young men are so trained that they can keep the injured man alive. For instance, an orthopaedic surgeon must be prepared to deal with an acute chest injury, as must a neurosurgeon in some remote parts of the country."

Dr. A. MONSAINGEON (France) said that entry to training as a surgeon in France was by competitive examination. The student began with the faculty and then did all his training in the hospital, becoming an assistant and then a chief of service. All this was by competitive examination, which removed the danger of outside pressure. A weakness in the system was that there was no possibility of a man's moving from one group of hospitals, say in Paris, to another group in the provinces, but steps were being taken to remedy this. Because of the keen competition, it was difficult for a man to become a surgeon and to obtain appointments unless he had been trained in one of the teaching hospitals. In the non-teaching hospitals he would not have the same chance to learn various branches of surgery.

Professor I. S. RADVIN (United States) said that in America there was a tendency for the system to become more rigid, and they were trying to find enough places where the young man going into the surgical specialties could also obtain an adequate training in general surgery.

Among the other problems mentioned was that of the maldistribution of surgical and other specialists in India. They had tended to congregate in the big cities. An attempt was being made to solve the problem by increasing the emoluments of those who went out to the districts.

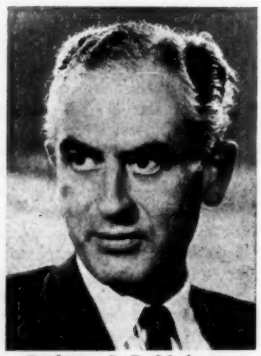
After the discussion, Professor CHAMBERLAIN said that there seemed to be no difference in the experience which the various countries demanded of their surgeons. "What is entirely different between this country and others," he continued, "is that we here give instruction and hold examinations, and for practical purposes it seems that no one else has spoken of having such a system in his country. The most important point which has emerged from the discussion is that everyone is very conscious of the need for practical experience before a man is allowed to take surgical responsibility on his own."

NOBEL PRIZE

The Nobel Prize for Medicine of about £15,000 is shared this year by Professor Sir Frank Macfarlane Burnet, O.M., F.R.S., director of the Walter and Eliza Hall Institute of Medical Research, Melbourne, and Professor P. B. Medawar, F.R.S., Jodrell professor of zoology and comparative anatomy, University College, London. The official citation says the award was made for their work on the problem of acquired immunological tolerance, and their contributions in this field are discussed on p. 1296.

Sir Macfarlane Burnet was born in Victoria in 1899 and was educated at Geelong College. He took his M.D. at Melbourne University and has spent most of his working life there except for two periods in England when he was Beit Fellow at the Lister Institute in 1926 to 1927, and a visiting worker at the National Institute for Medical Research, Hampstead, in 1932 to 1933. The Walter and Eliza Hall Institute, Melbourne, has claimed him for much of the rest of the time. He was assistant director there in 1928 to 1931 and 1933 to 1934 and has been director since 1944. He is also professor of experimental medicine in Melbourne University. The Royal Society has recognized his distinguished work by awarding him both the Royal Medal and the Copley Medal (the Society's highest award). He was knighted in 1951 and in 1958 he was appointed to the Order of Merit. Among his many other honours are the honorary Sc.D. of Cambridge University and Fellowship of the Royal College of Physicians. He has published many scientific and technical papers, and his books include *Natural History of Infectious Disease, Virus as Organism, Viruses and Man, Principles of Animal Virology, Enzyme Antigen and Virus,* and *Clonal Selection Theory of Acquired Immunity.*

Sir Macfarlane Burnet, O.M.



Professor P. B. Medawar.

Professor Medawar, who, it was recently announced, is to succeed Sir Charles Harington, F.R.S., in 1962 as director of the National Institute for Medical Research at Mill Hill, was born in Brazil in 1915. He was educated at Marlborough College and Magdalen College, Oxford, and was appointed senior research Fellow of St. John's College and university demonstrator in zoology and comparative anatomy in 1944. He became Fellow by Special Election of Magdalen College in 1946. He was appointed Mason professor of zoology in the University of Birmingham in 1947, and moved to his present position in 1951. He was elected to the Royal Society in 1949, being awarded its Royal Medal in 1959, and was appointed a C.B.E. in 1958. He has written many scientific papers on growth, ageing, immunity, and cellular transformations. Professor Medawar has paid tribute to the help given to him by two of his colleagues, Dr. L. Brent and Dr. R. Billingham, in the work for which the Nobel Prize was awarded.

The portrait of Sir Macfarlane Burnet is an Australian official photograph by Neil Murray; that of Professor Medawar is by Camera Press Ltd.

Nova et Vetera

AMERICAN COLLEGE OF SURGEONS

This book* tells the remarkable story of the foundation and progress of the American College of Surgeons. Dr. Loyal Davis, with the advantage of an intimate knowledge of the administrative working of the College and a personal friendship with many of the leading figures in its inauguration and development, has written a detailed and authentic account from original sources. It is an excellent history and one can scarcely call it a fault that occasionally the historian becomes an advocate.

In 1905 Franklin Martin, a prosperous, talented, energetic and confident 48-year-old gynaecologist in Chicago, conceived the idea that there was room and need for a new surgical journal which should "be edited by surgeons in practice," should "include within it articles in all the special fields of surgery," and should be called *Surgery, Gynaecology and Obstetrics.* That Martin had faith in his own capabilities was shown by the fact that he and his wife took a controlling proportion of the initial shares. He was justified, for the venture was an immediate success. In 1910, with a view to helping surgeons to see the work of the leaders in surgery, Martin was the main agent in the founding of the Clinical Congress of Surgeons of North America, which also proved an overwhelming success. That was the year in which appeared Abraham Flexner's *Medical Education in the United States and Canada,* a report which "struck a responsive chord" in the mind of Franklin Martin, whose alert mind now thought of a way to improve surgical education and practice in North America. He consulted George Crile, the brothers Mayo, J. B. Murphy, and other surgical leaders, and the result was the foundation of the American College of Surgeons. The object of the College was by all means in its power "to elevate the standard of surgery." Incorporation papers were taken out on November 25, 1912, and the management was eventually vested in 12 regents, 150 governors, a president, a general secretary, and a treasurer. J. M. T. Finney was elected the first president, A. J. Ochsner the treasurer, and Franklin Martin the general secretary. The inaugural meeting was held on November 13, 1913, when Sir Rickman Godlee brought greetings from the Royal College of Surgeons of England and delivered an inaugural address. There is no doubt that the new College owed something to the traditions of the English College, but it developed along very different lines owing to the special circumstances existing in America. It was extremely fortunate in having as its guiding spirit and organizing secretary a man dedicated to his task, of proved administrative capacity, and trusted by a large proportion of American surgeons. It was owing to Franklin Martin's genius that the College went from strength to strength until in 1935 he died, leaving behind him a strong organization which had already immensely raised the standard of surgery and greatly improved the efficiency of hospitals and the training of postgraduates in surgery.

We noted two slight errors. Thomas Percival was never knighted, and the *Lancet*, though certainly old and respected, does not represent the British Medical Association, which

**Fellowship of Surgeons. A History of the American College of Surgeons.* By Loyal Davis, M.D., F.A.C.S. (Pp. 523+vi. 84s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

is fortunate in publishing its own *British Medical Journal*. One other detail interested us. We noted that the Murphy Oration of the Clinical Congress became later the "Oration in Surgery," and later still "The Martin Memorial Lecture." Murphy and Martin had somewhat similar origins, both achieved greatness, and they were close and faithful friends. Would not the position best be met by calling it "the Martin-Murphy Memorial Lecture"?

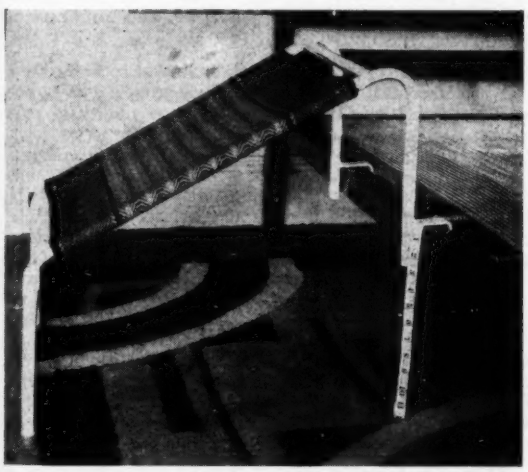
ZACHARY COPE.

New Appliances

AN INEXPENSIVE SUPPORT FOR POSTURAL DRAINAGE AT HOME

Dr. G. C. JACKSON writes: Postural drainage is recognized as a fundamental part of the management of chronic bronchitis and bronchiectasis. In hospital one can rely on Sister and the physiotherapist to ensure that it is performed regularly. At home it is very difficult to persuade milder cases to persevere with postural drainage when the latest chest infection is forgotten. The more severe cases experience such acute dyspnoea and general discomfort from postural drainage that they may be literally afraid of it.

In this second group are the patients with bilateral basal bronchiectasis, with some degree of emphysema and perhaps early cor pulmonale. They have a chronic chest infection which may respond well to antibiotics but may recur quickly when the antibiotics are stopped. There is often a long history of gradual deterioration. Pulmonary resection may have been considered earlier and rejected. They are unfit to hang over the bedside, while segmental drainage over pillows may not be effective.



For these patients I used to suggest various makeshift supports to lie on during postural drainage. The most satisfactory was an inclined ramp made by placing a chair under the foot of a bed. This does help, but, like all makeshift arrangements, it soon becomes an intolerable nuisance. One of my patients improved on this principle by designing for his wife a support which clips to the bed-frame. It is made of light steel tubing lashed with webbing. A pillow is tucked in the top for the patient to lie on. The frame is neat enough to be left in place, permanently ready for use.

These frames were first made last winter and were much appreciated.

One patient had needed treatment with antibiotics monthly last summer. Using the support to perform

(*Continued at foot of next column*)

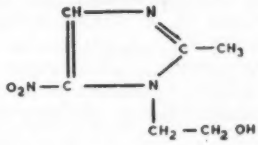
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Metronidazole

"Flagyl" (May and Baker).

Chemistry.—Metronidazole is 1-β-hydroxyethyl-2-methyl-5-nitroimidazole, and has the following structural formula:



Pharmacology.—Tests *in vitro* and *in vivo* have shown this drug to have considerable anti-trichomonal activity. In animal experiments its toxicity has been shown to be low. Normal growth of Döderlein's bacillus was obtained on medium including metronidazole even in a 1-in-300 concentration. In clinical use Döderlein's bacillus has been shown to reappear during treatment in association with a return to normal *p*H of the vagina. The drug has no action against monilia.

Therapy.—Metronidazole, given orally, is effective against infestation with *Trichomonas vaginalis*. The recommended dosage is one tablet (200 mg.) thrice daily for seven days. Careful clinical trials recently reported and discussed in this journal[1–4] indicate that this new drug provides a real advance in the treatment of human trichomoniasis. Local vaginal therapy is no longer necessary, and, for the first time, infected males can be treated equally easily and effectively.

Side-effects.—So far these have been both few and mild. Gastro-intestinal disturbance has been reported, but its incidence and severity are slight unless 600 mg. per day is exceeded; gastric irritation is reduced when tablets are taken with, or immediately after, food. A few cases of scarlatiniform eruption have occurred, but no case of blood dyscrasia has been reported.

N.H.S. Basic Price.—21 tabs., 16s. 8d.

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1 Watt, L., and Jennison, R. F., *Brit. med. J.*, 1960, 2, 902.
2 Rees, E., ibid., 1960, 2, 906.
3 Moffett, M., and McGill, M. I., ibid., 1960, 2, 910.
4 Ibid., 1960, 2, 922.

(*Continued from preceding column*)

postural drainage regularly for the first time, she was able to go through the winter without antibiotics. Another patient previously unable to tolerate postural drainage found that by draining more often, up to eight or ten times daily, she seemed able to abort a new chest infection.

Many patients who would benefit greatly from postural drainage are prevented by their disability from performing it in the usual ways. The support described has proved practicable even for a patient who needs a portable oxygen apparatus for walking more than a short distance. Regular use of the support has seemed to allow some economy in the use of antibiotics.

The support would be of no value to a patient having a localized area of bronchiectasis suitable for resection.

The use of shoulder supports was considered, but they have not been necessary. The existing frames have been made to fit each patient's bed, even allowing for the depth of the mattress when compressed by the patient's weight. The legs could easily be made to adjust in height to fit any bed reasonably well.

My thanks are due to Mr. Salisbury, of Whittle-le-Woods, Lancs, who designed and made the frames.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Concept of Collagen Diseases

Sir,—I feel I must take issue with you on the historical accuracy of the second paragraph of your excellent leading article "Auto-antibodies and Lupus Erythematosus" (October 15, p. 1141). I do so, not for reasons of pedantic criticism, but because the reasoning in this paragraph reveals a misconception, widely held, and one which is likely to impede a proper understanding of the pathogenesis of disease involving the connective-tissue system.

You say, and a similar observation has been made by E. G. L. Bywaters[1] and others:

"P. Klemperer's use of the term 'collagen diseases' drew wider attention to the similarities between disseminated lupus and rheumatoid arthritis, dematomyositis, and polyarteritis, in all of which widespread fibrinoid necrosis of collagen may occur. The term is now obsolete, since necrosis of collagen may be seen in any destructive process, such as abscess or peptic ulcer. . . . If, therefore, the concept of a diffuse collagen disease is no longer tenable, the theory that disseminated lupus (and related disorders) results from generalized auto-immune reactions becomes more attractive."

Now, of course, this is almost a complete antithesis of the epoch-making concept put forward by Klemperer, Pollak, and Baehr[2] in 1942 and developed by Klemperer and his associates in subsequent years. The misconception can only be attributed to the fact that too few have read this little essay of about 1,400 words, which appeared in the *Journal of the American Medical Association* for May 23, 1942.

Klemperer and his colleagues started by pointing out the difficulties that a strict Morgagnian or visceral concept of the location of disease processes can cause in the understanding of certain disorders, and that it might be more profitable to adopt Bichat's concept of tissues. They take as an example rheumatic fever, which had been shown by Klinge and his school to affect the connective tissue throughout the body, and go on to say, "The apparently heterogeneous organ lesions in disseminated lupus erythematosus have similarly been shown to be the result of a fundamental alteration of the collagenous tissues. . . . It is reasonable, therefore, to consider these maladies as systemic diseases of the connective tissues. The justification for the concept of a systemic disease of the connective tissues depends on the actual existence of a connective tissue system." Then, following H. Schade's[3] concept of the physiochemical nature of connective tissue, they illustrate its metabolic as well as structural significance and participation in general pathological processes.

They then show that not only are there widespread connective-tissue changes in disseminate lupus but also in scleroderma, but emphasize the paradox that the "morphologic alterations are hardly crucial enough to account for the profound clinical debasement and death of the patient" and raise the question, "Can we assume therefore that a derangement of the colloidal state of the entire collagenous system exists, though it cannot be consistently revealed by our histologic methods?" Klemperer and his colleagues then point out that although a number of diseases may affect the connective-tissue system, "however, to identify this system as the seat of certain diseases is by no means to identify these diseases with one another or even to relate them. This would be an unjustifiable over-simplification." In this context they discuss R. Roessle's[4] concept of the "rheumatische formenkreis," linking together rheumatic fever, periarteritis nodosa, and thromboangiitis obliterans as allergic conditions on the basis of the fibrinoid changes, but they suggest that this is unjustified as there is no universal acceptance of the allergic nature of rheumatism, the prototype of the group, and, though "it has been shown experimentally that hyperergic inflammation is characterized by fibrinoid degeneration of collagen, the converse does not necessarily follow, that widespread fibrinoid degeneration always indicates a state of hypersensitivity. We know that local fibrinoid degeneration of collagen is found in a variety of states not related to hypersensitivity. It is reasonable to assume, therefore, that widespread collagen degeneration may also be the result of causes other than hypersensitivity," and the sex differences in D.L.E. and scleroderma speaks against hypersensitivity as the sole mechanism. Klemperer ended this prescient essay thus: "Until now an inordinate preoccupation with immediate cause has shut the door to an analysis of the fundamental changes within the connective tissues considered as a colloid system. The connective tissues having been established as the seat of certain diseases, it remains for the investigator to explore this system with methods available to the biophysicist and the chemist."

Little attention was paid to Klemperer's paper, but A. R. Rich[5] in his Harvey lecture suggested, in analogy with his experiments indicating an allergic mechanism for periarteritis nodosa and rheumatic fever, that D.L.E. might also be due to tissue hypersensitivity, a view strongly opposed by the Mount Sinai group. It was not until 1949, with the introduction of cortisone, and its apparent efficacy in D.L.E., dermatomyositis, scleroderma, polyarteritis nodosa, etc., that the term "collagen disease" was popularized and misapplied. Klemperer[6] ruefully wrote in 1950:

"A never-relaxing concentration upon these problems has convinced me that the concept of collagen diseases is not an idle speculation; but the impatience of clinical investigators and a peculiar worship of diagnostic terms have led to an exaggerated popularity of the diagnosis collagen disease. There is a danger that it may become a catch-all term for maladies with puzzling clinical and anatomical features. It is not a term applicable to diagnosis and certainly does not define the morbid processes of the diseases grouped together. All we wanted to express originally was that in certain diseases anatomical investigations reveal conspicuous alterations of the intermediary substances of the connective tissue in a systemic manner. These morphological disorders are only outward manifestations of morbid processes, the site and nature of which are still obscure. When further basic research has clarified the factors which control the plasticity of the connective tissues under normal and abnormal conditions, the concept of collagen diseases will have well served its purpose."

Thus, Sir, I would suggest that Klemperer's concept of the collagen diseases, far from being obsolete, is as apposite to-day as it was 18 years ago. The pathogenesis of disseminate lupus erythematosus still remains obscure; it may well be that the biochemical lesion is to be found in the nucleus of mesenchymal cells, and the consequent intracellular metabolic disturbances, as Klemperer suggested in his Harvey lecture,[7] results in the deposition from the blood stream of abnormal proteins in the ground substance, producing the tinctorial change which is known as fibrinoid, and in the immunological reactions characteristic of this disease. Immunologists are coming, somewhat unwillingly, to the conclusion that there are not just two types of allergic reaction—the immediate or anaphylactic type and the delayed or tuberculin type. The elucidation of the

pathogenesis or aetiology of collagen disease also demands a new approach, free from morphogenetic preconceptions, but based on a proper understanding of the functional significance of connective tissue, of which an excellent review was provided by Sir John Richardson at the Middlesbrough symposium (October 15, p. 1147).—I am, etc.,

Radcliffe Infirmary, Oxford. A. H. T. Robb-Smith.

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2 Klemperer, P., Polak, A. D., and Baehr, G., *J. Amer. med. Ass.*, 1942, **119**, 331.
3 Schade, H., *Die Physikalische Chemie, in der Inneren Medizin*, 1923. Steinkopf, Dresden.
4 Roessle, R., *Virchows Arch. path. Anat.*, 1933, **288**, 780.
5 Rich, A. R., *Harvey Lect.*, 1947, **42**, 106.
6 Klemperer, P., *Amer. J. Path.*, 1950, **26**, 505.
7 —— *Harvey Lect.*, 1955, **49**, 100.

Folic-acid Absorption Tests

Sir,—I have read with much interest Dr. J. Badenoch's excellent Goulstonian lectures on "Steatorrhoea in the Adult" (September 24, p. 879, and October 1, p. 963) and Dr. I. Chanarin's claims for the superiority of folic-acid absorption tests that involve the measurement of serum levels after a test dose (October 15, p. 1160). Measurement of the serum or urinary level of folic acid after an oral test dose does not in itself give evidence of malabsorption of folic acid, since a low level may merely indicate folic-acid depletion, but no doubt the patients with regional enteritis referred to by Dr. Chanarin were "saturated" with folic acid before the absorption tests were done and the extent of the disease assessed by laparotomy.

In general my experiences with serum tests of folic-acid absorption have been unfortunate, despite promising results at an early stage,[1] and I am surprised to read that "patients with malabsorption syndrome who show peak serum folic-acid levels between 25 and 40 μmg./ml. after 2 to 3 mg. by mouth usually excrete normal amounts of folic acid in the urine when given 5 mg. of the vitamin," although admittedly I have not investigated this specific point. However, in a recent investigation, when eleven cases of primary malabsorptive disease (idiopathic steatorrhoea) were given an oral test dose of 3 mg., the peak serum level was less than 50 μmg./ml. in only four, but the urinary output was lower than in control cases in all eleven instances. After "saturation" with folic acid the tests were repeated in nine of the patients, a dose of 40 μg./kg. of body weight now being used. Again the serum tests showed low levels in only four instances, and there was no correlation with urinary results.

To complicate the matter further, oral treatment with folic acid for four weeks (and perhaps for shorter periods) may restore folic-acid absorption in primary malabsorptive disease to normal, so that any test of folic-acid absorption may give normal results because of folic-acid therapy. This objection may not apply to such tests in regional enteritis, but, in general, tests involving only the measurement of serum or urinary levels after an oral test dose of folic acid are not of value unless the patients are first "saturated" with folic acid, and the giving of *too much* folic acid (a quantity yet to be established) may invalidate the test.

After having spent a considerable time using tests that involve the measurement of serum levels after an oral dose and those in which the urinary output after injected and oral test doses are compared,[2 3] I find the latter more satisfactory for practical use, since the results are more easily interpreted and prior "saturation" with folic acid is not usually required. It should be realized, however, that too much must not be expected of any test of folic-acid absorption, and that the results must be considered in relation to the clinical picture, the results of other tests of absorption, and the findings obtained by *x*-ray examination of the small intestine and by jejunal biopsy.—I am, etc.,

Department of Medicine, Edinburgh University. Ronald H. Girdwood.

References

1 Girdwood, R. H., *Proc. Nutr. Soc.*, 1955, **14**, 41.
2 —— *Quart. J. Med.*, 1956, **25**, 87.
3 Cox, E. V., Meynell, M. J., Cooke, W. T., and Gaddie, R., *Gastroenterology*, 1958, **35**, 390.

Megaloblastic Anaemia of Pregnancy

Sir,—The important paper, "Clinical Analysis of 100 Cases of Severe Megaloblastic Anaemia of Pregnancy," by Drs. P. B. B. Gatenby and E. W. Lillie (October 15, p. 1111) merits careful consideration by all obstetricians. In the discussion, however, they make statements which require further clarification. They write:

"The prevention of megaloblastic anaemia by the routine administration of folic acid in pregnancy would seem an obvious solution to this problem. Some have accepted this principle (Lowenstein *et al.*, 1955; Francis and Scott, 1959). The main disadvantage in the prophylactic use of folic acid therapy is that megaloblastic anaemia not caused purely by the demands of pregnancy will be masked and lead to delay in recognizing the underlying cause. . . . Again, there is always the possibility of an Addisonian anaemia being masked, and it is well known that folic acid may precipitate serious neurological changes."

There seems to be fairly general agreement that folic acid is curative in this condition, and it is of course true to say that when it is administered to a patient who also has an achlorhydria and is suffering from true Addisonian anaemia, then vitamin B_{12} will quickly become depleted by erythropoiesis. As a result subacute combined degeneration of the spinal cord may thereby be precipitated.

The authors do not, however, make it clear that Lowenstein, Pick, and Philpott administer vitamin B_{12} as well as folic acid to their pregnant patients. In 1953 they decided to add 1 μg. of vitamin B_{12} and 1 mg. of folic acid to each tablet of the proprietary supplement of ferrous sulphate and ascorbic acid prescribed during pregnancy (3 tablets daily). Writing in December, 1955, they state that since the introduction of this treatment no new cases of megaloblastic anaemia had been found.[1]

These satisfactory results are in marked contrast to those of C. G. Berry,[2] who studied 30 cases of severe anaemia of pregnancy in Lagos. Most of these were macrocytic hypochromic anaemias, frequently complicated by liver disease and parasites in the blood or intestine. In spite of administering iron, liver, and folic acid the majority of these pregnancies ended in abortion. Berry concludes that although the primary defect in megaloblastic anaemia may be non-availability of folic acid the Nigerians appear to suffer from a deficiency of extrinsic factors in addition, and as a result there will be no response to folic acid until this has been corrected.

Drs. Gatenby and Lillie are to be congratulated upon a most interesting and important clinical study. One cannot help wondering whether their researches at the Rotunda Hospital may not act as a stimulus to other

workers in England and Scotland, and lead to the recognition of megaloblastic anaemia as a relatively common complication of pregnancy.—I am, etc.,

St. Austell, Cornwall. D. G. Wilson Clyne.

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[1] Lowenstein, L., Pick, C., and Philpott, N., *Amer. J. Obstet. Gynec.*, 1955, **70**, 1309.
[2] Berry, C. G., *Brit. med. J.*, 1955, **2**, 819.

Ferrous Fumarate and Occult Blood Tests

Sir,—We were somewhat perturbed to see (October 8, p. 1084) your note on ferrous fumarate under the heading of "To-day's Drugs." Attention was drawn by Dr. D. G. Illingworth in a letter to this journal (November 21, 1959, p. 1099) to the resulting false-positive occult blood tests, by the orthotolidine method, which frequently occurred during administration of this preparation.

For some months in the Chester Hospitals we had many unexplained positive occult blood tests (by the orthotolidine method) on patients having iron medication, with much resultant confusion in treatment and some prolongation of hospitalization. Attention was then drawn to Dr. Illingworth's letter, and on inquiry it was found that the principal iron preparation in use was ferrous fumarate. Cessation of its use has resulted in the disappearance of the unexplained positive occult blood tests. The ease with which false-positive occult blood tests can be produced was demonstrated by administering it to four healthy antenatal patients, three of whom developed strong positive orthotolidine tests within three weeks. Any publication of information concerning this preparation should be accompanied by a warning of the liability to produce positive occult blood tests. In our opinion this liability so detracts from the value of this preparation, by interfering with diagnosis and treatment, as to make it an unsuitable preparation for regular use.—We are, etc.,

T. D. S. Holliday.
Chester. I. M. Cuthill.

Hypophysectomy and Breast Cancer

Sir,—Dr. John Nabarro in his letter (October 8, p. 1087) discussed surgical hypophysectomy only in terms of the transcranial operation. In several centres in this country transnasal surgical hypophysectomy is being developed following the lead of Riskaer in Copenhagen and Hamberger in Göteborg. At St. Thomas's Hospital I have performed 40 transnasal hypophysectomies in the past 15 months, and in uncomplicated cases it involves a stay of only two to three weeks in hospital and causes minimal disfigurement. In my experience the patient suffers less pain in the post-operative period than the patients who have had an yttrium-90 implantation. It is my impression that a hypophysectomy can be performed by the transnasal route without great risk to the patient and without a prolonged stay in hospital. If this is confirmed it removes most of Dr. Nabarro's objections to the operation as detailed in his letter.

To my mind the great disadvantage of the implantation of irradiated material is that the surgeon does not know the size of the organ he is irradiating. He measures the pituitary fossa by radiology and acts on the assumption that the pituitary fills the fossa. Oppenheimer[1] showed that this is not always a correct assumption.

Among my 40 patients there are 10 with diabetic retinitis, and the transnasal route makes this a comparatively simple, safe, and satisfactory operation. "Pitressin" (vasopressin) injections are often needed for the first few weeks, but after this snuff controls the polyuria until the need for it disappears after a few months. The surgical technique and the results have not yet been published, because a considerable time must pass before the results can be assessed.

It is my opinion that surgical hypophysectomy is a sounder proceeding than the implantation of irradiated material.—I am, etc.,

London W.1. Geoffrey H. Bateman.

Reference

[1] Oppenheimer, D. R., *J. Laryng.*, 1959, **73**, 670.

Lumps in the Breast

Sir,—Dr. Charles Mills (October 15, p. 1162) quotes the case of a long-standing clinically innocent lesion of the breast which was found, on exploration, to be malignant. Despite radical mastectomy "under difficulties" the lady died of disseminated disease eighteen months later. In the view of Dr. Mills the tragedy of this case is that for a period of years she had been reassured by a succession of physicians and surgeons; his golden rule of "cutting down and having a look" was thus disregarded and the opportunity to cure was lost.

Whilst agreeing that this is a possible, though unlikely, conclusion, it is surely equally fair to believe that the patient in question might well be alive to-day if the London surgeon had followed the example of the others and given the lady another pat on the back.

Breast cancer is unpredictable and expectation of life very largely depends on the inherent potentiality of the tumour to metastasize. Some lesions do so before they are clinically palpable as lumps, whilst others are content to remain relatively quiet, if left severely alone, in their sites of origin. These well-known facts answer Dr. W. M. L. Horner's remarkable observation (October 15, p. 1162) that "advanced neoplasms would not arise if the original lump had been excised in the first place."

It is a great pity cancer propagandists and educationists dwell so much on breast disease. They would do better to confine their arguments to suspicious early lesions arising from epithelial tissues, lesions which are relatively well behaved and justify urgent radical treatment every time.—I am, etc.,

Hull Royal Infirmary. K. W. Beetham.

Hypnotic Treatment of Asthma

Sir,—Dr. D. Davies (October 8, p. 1092) raises an interesting point as to whether hypnosis contributed to the death of the patient in the case he described, but, from the account of the case history, hypnosis may have had nothing to do with this patient's sudden collapse and subsequent death. The description is compatible with a history of a patient who has been on long-term corticosteroid therapy for asthma. If the corticosteroids are gradually reduced (as was the case with the patient in question) he may remain well for a number of weeks or months and then relapse into severe status asthmaticus which may be fatal, particularly if corticosteroids are not used in the treatment. From Dr. Davies's description, the patient received subcutaneous adrenaline and hypnotherapy, but apparently

was not recommenced on steroids. Patients who have been on long-term steroids are frequently unable to adapt to stressful situations such as status asthmaticus, and they may suddenly collapse due to suprarenal suppression. One of us (R. S. B. P.) has had the experience of four cases which relapsed into status asthmaticus within two months of withdrawal of corticosteroids after long-term treatment. There were three fatalities, none of whom received corticosteroids, within 48 hours of admission; the case which recovered was treated with corticosteroids (in large doses) on admission to hospital.

It would seem imperative that if a patient, after long-term steroid therapy, is tailed off his drugs and then develops status asthmaticus even as long as two years later, he must be treated with corticosteroids, and these should be given intravenously, as intramuscular preparations have a moderately slow rate of absorption.—We are, etc.,

R. S. Bruce Pearson.
Lionel Fry.

King's College Hospital, London S.E.5.

Sir,—Dr. D. Davies (October 8, p. 1092) suggested that hypnosis may have been responsible through oversedation for the death of his patient. It is usually found that asthmatics are so relaxed under hypnosis that they are able easily to get rid of the bronchial secretions. It is therefore not likely that the plugging of the small bronchi and bronchioles would be the cause of death.

The most probable explanation is that the continuous steroid therapy, producing a "pharmacological adrenalectomy," was responsible for the fatal outcome. According to Brockbank,[1] steroids are not so good in chronic asthma: "Although initial improvement was good, deterioration took place after several months of treatment. Seven patients had died unexpectedly, possibly as a result of adrenal atrophy." This is what probably happened in Dr. Davies's case.—I am, etc.,

London S.E.25. A. Fry.

Reference

[1] Brockbank, W., *Brit. med. J.*, 1958, 2, 154.

Post-operative Obstruction Caused by a Swallowed Hair-grip

Sir,—Post-hoc, propter-hoc judgments are responsible for an untold amount of inaccurate and slipshod medical teaching. The letter that has appeared in your journal under the above heading (October 15, p. 1161) would seem to be a classical case in point. A patient develops some post-operative ileus following a hysterectomy, a not uncommon thing to happen, and usually thought to be due to some blood collecting in the pouch of Douglas. A slightly infected haematoma would account for the leucocytosis. A skiagram shows fluid levels in the bowel, as one would expect, and reveals a hair-grip in the descending colon. The writer then makes the astounding statement that this solves his dilemma. What possible justification is there for associating the ileus with the hair-grip? When the ileus was overcome, and the bowels began to move, the hair-grip was passed. Why not? Of all ingested foreign bodies hair-grips are perhaps the commonest, because most women are in the habit of holding them in their mouths. I have seen them in the alimentary tracts of women of all ages and of very young children, who copy their mother's habits. In my experience they are always quite innocuous, although I know that this view is not universally held. All those I have seen have been passed without incident, although some have been slow. On one occasion I watched one for nearly two months before it was passed. Please let us adopt the British practice of regarding a man innocent until proved guilty.—I am, etc.,

Farnham Common, Bucks. Robin Burkitt.

Migratory Pruritus

Sir,—I am attending a male patient, aged 35 years, of a slightly neurotic disposition, who suffered from intractable pruritus ani for the past 20 years. The patient had, some years ago, *x*-ray therapy, which gave temporary relief. About a year ago he had a severe emotional crisis, precipitated by a domestic upheaval. During this time the pruritus ani ceased and he developed around his mouth a dry eczema, and also a pruritus in the region of his mouth and nose. After some weeks the eczema in the region of his mouth cleared up, but the pruritus around his mouth and nose has persisted. The patient finds the present site of the pruritus more bearable than the pruritus ani. He finds best relief from the application of a simple face cream.

The transference of the site of pruritus due to psychological causes induced by an emotional crisis is, I consider, of special interest.—I am, etc.,

Michael J. Keating.

Guanethidine and Tolerance

Sir,—I was very much interested in Dr. A. K. Pittman's letter (September 10, p. 804) in which he disagreed with Dr. D. G. Julian about the development of tolerance with guanethidine therapy in hypertension (August 27, p. 660). Recently after having followed about 25 cases of hypertension being treated with guanethidine in this hospital for more than four months I have discovered two cases in which tolerance has developed with this drug. In both these cases we had to gradually increase the dose of guanethidine to lower the blood-pressure to previous levels. I would agree with Dr. Pittman in saying that incidence of tolerance with this drug so far in my limited experience has been much less than with bretylium in the treatment of hypertension.—I am, etc.,

The General Hospital, Birmingham 4. S. P. Singh.

School Phobia

Sir,—In viewing school phobia there are two issues. (1) The handling of the presenting symptom—namely, refusal to go to school. (2) The investigation of the personality. It appears to us that these are separate issues and that return to school is necessary before any real investigation can begin. In addition, if this is successfully achieved, then there is ego-integration, and both parents and children are better equipped for examining unconscious mechanisms. Up to date we have not found it necessary to send children to boarding school because of refusal to attend school. To do so would in our view mean rejection of the child and an admission of failure on the part of the parents. In addition it would create a loophole whereby parents could possibly send their children to boarding school at the cost of the local education authority.

There is no doubt about the urgency of these cases. They are treated as emergencies in our clinic. One came

to us after attempted suicide, another under escort from the remand home where he had been committed for non-attendance at school. In neither case was there any evidence of separation anxiety. In our experience this seems to be generally the case. Both returned to school under pressure. In one (the latter) force was in fact used. Two welfare officers escorted the boy to school. When this child returned to school the associated symptoms of headache, sickness, and dizziness cleared up. This happened in most of the cases. In addition there was a marked improvement in his behaviour. The field was now clear for an investigation of his personality. His mother was seen and the problem of retardation in his school work was discussed. We suggested that this should be investigated, and asked her to put the question to her son: Would he come along for further tests? The following week the mother reported that he replied he would come because we said he did not have to. Thus he developed a positive relationship to the clinic despite the fact that we had instigated firm handling by the two welfare officers. It is also to be remembered that it is much more difficult to gain a relationship with children when they have been directed to attend the child guidance clinic by the court. An added feature which frequently happens is that of delay in referral. He was seen originally by the family doctor six years ago, referred to hospital, and fully investigated. His mother stated she was told that the troubles were due to nerves and unhappiness at home, and nothing therefore could be done. Had this case been seen by us at that time we would have been placed in a more satisfactory position for handling it and before it became an emergency, as is the case in so many instances.

On examining the records of the clinic we find there have been only one or two failures in obtaining return to school in a considerable number of cases during the past 14 years. The following factors were present in the successful cases. (1) Parents were able to admit to the presence of guilt, and that it was wrong for children not to attend school if medically fit. In the first case quoted, guilt over not going to school might have been *one* factor leading to depression and the suicidal attempt. (2) There was the need to recognize the associated symptoms and tensions in the proper perspective, their severity being neither exaggerated nor underestimated. (3) Parents co-operated and agreed that firmness was required with the presenting symptom even to the extent of using force. For example, before the welfare officers exerted force the parents' permission and agreement were obtained. (4) There was the requirement to live with the symptoms in the proper spirit until their resolution could be achieved. This not only involved the child and the parent but also the family doctor, the consultant, the teachers, probation officers, welfare officers, and other members of society who might become involved in the situation. Thus in the acute phase there is frequently the need for co-operation between different members of society. (5) There was a movement in the parents towards love of the type that included sympathy plus firmness and the ability to stand the stress of the different emotions involved.

It seems a lamentable fact that so little is known of what goes on in child guidance clinics, and it is gratifying to read and express opinions in your columns on one aspect of the work that we meet with.—We are, etc.,

R. Warnecke.
Sheffield. D. Lawrence.

Sir,—In your admirable leading article on "School Phobia" (September 17, p. 848) stress was laid on the chronic state and the long-standing neurosis of mother or child, but no differentiation was made from the much commoner acute syndrome. I agree that insistence on school attendance or residential schooling is necessary in most of the former cases, but could be harmful in the latter type of child.

An acute anxiety state suddenly appears in a child hitherto regarded as normal, triggered off by some minor incident or an accumulation of trivial traumatic events often including the death of some relative, friend, or pet, and almost invariably occurring in the pubescent period. The majority of these cases are overlooked because persistent refusal to go to school is rare compared with the many children who are merely reluctant whilst in this state. School phobia may be overshadowed by other symptoms such as anorexia nervosa, insomnia, obsessional states, or even suicidal attempts. Depressive traits, guilt, sense of unworthiness, lack of self-confidence, and fear of competition, criticism, or of the future are characteristic features of this state. Rationalization and transference may focus on arithmetic or a particular teacher, but it is usually obvious that the anxiety is spread over all fields. These children cling to mother as any sick child will do, "but only when I am like this," as one girl explained. Sudden recovery may follow, as in another girl on her thirteenth birthday, and then was "better than ever before." There can be little doubt that the pubescent child may have affective disorders comparable to those seen in the climacteric, and like them due to both physiological factors as well as psychological. The emotional instability of puberty between the age of 10 and 15 is well known to every parent and doctor.

Treatment of acute anxiety at any age must begin by relieving the tension and avoiding any procedure which might increase it. Psychological investigation should not hold up these immediate steps. If a child reacts to school by vomiting or other psychosomatic symptoms of panic, it is obvious that insistence on school attendance is harmful, and a medical certificate will go far to relieve the child's guilty feelings. This type of child may have as much anxiety about being absent as attending, but should be regarded as being sick, even though the illness is psychological rather than physical. Such a child will tend to return to school on his own volition when he feels better, if he has been properly treated. The child psychiatrist is the proper person to deal with these cases, and the child guidance clinic, like any hospital, must be prepared to deal with emergencies in spite of waiting-lists, and these cases must be seen immediately. The family doctor should contact the psychiatrist as soon as possible. Referral through the official channels is often too slow and cumbersome.—I am, etc.,

Bramley, Near Rotherham. Patrick J. Crowley.

Sir,—I feel one aspect of this matter has been overlooked by your correspondents to date. Unfortunately there are still a few schools run by what one can only call sadistic-minded people, and therefore this possible factor, I feel, should be borne in mind before placing the blame squarely elsewhere.—I am, etc.,

London W.1. Peter Gilbert.

Cat Phobia

Sir,—Drs. H. L. Freeman and D. C. Kendrick are to be congratulated on the recovery of their patient with cat phobia (August 13, p. 497) and also on the open-mindedness with which they allow for alternative explanations of the patient's improvement. One possible explanation of the improvement is that the graduated exposure to the phobic stimuli permitted and in a sense forced improved discrimination between the original traumatic stimulus and the objects, chiefly cats, which

had acquired through generalization the capacity to evoke anxiety in the patient. From the data reported, it seems possible that the patient's fear of her father became markedly intensified when he drowned the kitten in the patient's presence. Cats may have thus come to remind the patient unconsciously of her father whom she feared. As usually happens, the avoidance of the cats reinforced them as phobic stimuli. In addition, the patient's preoccupation with cats may have prevented her from experiencing the more important (when she was young) fear of her father. The reports of the patient's dreams of her father during the treatment suggest that she was thinking much about him at this time. I suggest that during the treatment she gradually came to discriminate better the original, realistic fear of her father and the associated fear of cats. With the full realization that cats had never harmed her, but merely reminded her of her father, she lost her fear of them.

Two earlier reports of the successful treatment of cat phobia harmonize with this explanation. These were also instances of long-standing cat phobias. Under hypnosis the patient recalled in each case the original traumatic situation in which cats had been involved through association with a feared person or situation. In one case the patient had been frightened by her grandfather, who told her when she was 4 years old a gruesome story about a musk rat; the fear of cats (manifested as an irrational antagonism to them) occurred through their traditional association with rats.[1] In the other case the patient had associated cats' tails with masculine (penis-wearing) women of which her mother was one type and a person the patient much feared.[2] It is worth noting that in both these cases complete recovery immediately ensued when the patient recalled fully the relevant childhood experiences. In one case this was accomplished in one session, and in the second case after two sessions. The treatments were therefore even briefer than that of the patient reported by Drs. Freeman and Kendrick.

We now have ample evidence from the work of Dr. Wolpe and others that recovery from psychoneuroses can occur without de-repression of past traumatic experiences. At the same time it is important, as we make further advances, to add these to what we already know and not regard them as necessarily superseding previous observations. De-repression can be extremely helpful in aiding recovery from psychoneuroses and so can the review by the patient of significant painful experiences which have not been repressed. In either case, the recall of the repressed memories or the review of remembered ones may improve discrimination between what was once dangerous and the environmental stimuli which became accidentally associated with the original stimulus of fear.

The two cases I have cited show that psycho-analysis (or at least hypno-analysis) has had its successes in the treatment of cat phobia. Dr. E. Glover (August 27, p. 671) would have contributed more to the discussion of this topic if he had avoided *ex cathedra* statements about the intactness of the patient's conflicts and had cited, as no doubt he can, other specific cases in which de-repression has brought about recoveries from animal phobias.—I am, etc.,

IAN STEVENSON.

Department of Neurology and Psychiatry,
School of Medicine,
University of Virginia.

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[1] Erickson, M. H., and Kubie, L. S., *Psychoanal. Quart.*, 1939, **8**, 471.
[2] Schneck, J. M., in *Experimental Hypnosis*, 1952. Macmillan, New York.

Child Psychiatry

SIR,—I have read with personal interest the correspondence dealing with the use of married women in child psychiatry. The practical understanding of family health which is engendered by raising one's own family and by talking with other mothers as a mother and not as a doctor, combined with sound psychiatric training, should indeed produce a person invaluable in the field of child psychiatry.

Dr. W. Warren (October 1, p. 1017) suggests that the patience required for the years of part-time training might be a deterrent. In fact, such part-time training, if non-resident, would open the doors to a married woman with a family, removing some of the frustrations of the woman who wishes to give time to her family without completely abandoning her career. At present the only satisfactory openings are in public health, which is not every woman's choice, although often welcomed financially.

The conclusion of training would coincide with the growing of the family, and as a fully trained child psychiatrist she may well practise full-time, benefiting herself and the State service. I propose to investigate the possibility in my own area.—I am, etc.,

Wymondham, Norfolk. KATHERINE B. WORLEY.

Psychiatry in General Practice

SIR,—I am surprised to find such a faithful disciple of Dr. Michael Balint as Dr. Philip Hopkins (August 20, p. 601) ignoring one of the teacher's main precepts, that the most powerful drug which the doctor uses is himself. Dr. Hopkins believes that it is "interpretative psychotherapy" which helps his patients; Dr. L. M. Franklin believes more in pills (August 6, p. 451). I suspect that they are both using similar drugs called "Hopkins" and "Franklin," and that their long-term results will turn out to be very much alike. If I may echo what Balint and others have said before, we must find out how these drugs of the "interested doctor" group work, how they can most effectively be used, and indeed whether it is correct that in the long run they all produce similar results.—I am, etc.,

Waroona, West Australia. PAUL MESTITZ.

Development of Live Polio Vaccine

SIR,—Dr. Hilary Koprowski (October 15, p. 1165) is very severe, and at times offensive, in reply to Dr. D. E. Jeremiah's critical letter (August 6, p. 468). He does not deal with his main point, which was that it was reprehensible to use in any trial people who had not volunteered. I would have thought one could accept this view of human rights without being railed at as a reactionary.—I am, etc.,

Manchester. A. S. DUNN.

British Medicine Overseas

SIR,—During the course of my frequent travels to countries both inside and out of the Commonwealth, including several which were formerly under British or other colonial rule, I have observed with regret the declining influence of British medicine and the absence in the field of British doctors. During such travels I have met many medical colleagues from West Germany, Scandinavia, Jugoslavia, and other European states who

are working in the medical services of countries which have a need to employ foreign doctors: in some instances special arrangements appear to have been made for the recruitment of suitable doctors for such countries, sometimes through the various medical associations. The few British doctors whom I have come across are mostly working with religious missions or in special types of practice, such as with commercial concerns. In the training field Americans are very active everywhere, and it is, by and large, American methods which are being adopted by developing countries for the training of doctors, paramedical and other health workers.

My impression of British medicine is that it now seems not to be very interested in what is going on in the less-developed countries of the world. This has also been my own observation in Great Britain during the several visits which I have made to that country during the past three or four years. I would like to think that I am wrong, but my impression is that British medicine has turned in on itself and, if I may be pardoned the expression, is busily meditating on its own navel. Overseas friends of mine tell me that British medical youth appears to have lost its sense of adventure, and that perhaps the urge for security, as exemplified by the Welfare State and its facilities, has dimmed that interest in the welfare of the hundreds of millions of their fellow human beings which has traditionally been a feature of the British.

Perhaps it is true that the Overseas Medical Service, concerned as it is with the rapidly shrinking Colonial empire, no longer appeals to young doctors owing to the very insecure nature of the service. Perhaps it is also true that competition for places in the National Health Service plays a part in the present disinclination of young doctors to enter service abroad. Certainly it would seem that unless he has served in it and is on some form of secondment, the chances of a doctor getting into the National Health Service after a period abroad are very slim indeed. There is also the fact that many governments in the less-developed countries pay such low salaries to their own nationals that foreigners would not be able to accept them. This is far from being a general rule, however, and some countries which I know and which still rely almost entirely on foreign doctors to staff their services pay very good salaries indeed. Again, in one case at least, the country which was providing doctors made them a good allowance so long as they were in the recipient country, this being a form of contribution to that country's development.

I believe that British medicine could make a major contribution if our medical schools took a really active interest in the new medical schools which are developing in the less-well-placed countries of the world, and particularly in the Commonwealth. I am aware that something is being done in Africa, but the over-all effort is not very great, and I know of none of our great medical schools which are participating in this effort. Much could be done if our medical schools were to adopt newly formed medical colleges overseas: an exchange of staff would benefit not only the teachers in new medical colleges by introducing them to modern teaching methods and standards, but would also benefit the teachers in our own medical schools by introducing them to situations of which they are in all probability hardly aware. Medical practice in many countries is basic to a degree which is simply not seen in Great Britain to-day, where medical practitioners would hardly know how to deal with some of the simple conditions which remain the scourges of hundreds of millions of our fellow men at the present time. Teaching methods and hospital standards in new medical colleges and their associated hospitals would also greatly benefit by the introduction to them of teachers from old and well-established medical schools. I believe that, between them, the National Health Service and the medical schools could arrange for exchanges of staff at, for instance, the registrar level at any rate. I do not think that the medical schools should stand on their dignity and wait to be asked: they have a great contribution to make and should seek out the best ways of making it.

Another need which might possibly be met by the British Medical Association itself is for the establishment of a bureau to which could apply not only those doctors who wish to serve for a period abroad, but also those governments who wish to recruit doctors for their medical services. I know of no such organization in Great Britain, but if it exists then I apologize for referring to the need and can only say that it receives little publicity. I need hardly say that for obvious reasons the Colonial Office is not a suitable department to play any part in such activities, whereas possibly the Commonwealth Office might have a useful part to play. I have on several occasions been asked by young doctors in Great Britain how they can get to know of independent countries whose medical services offer the possibility of employment, and have had to reply that at present they must look out for advertisements in the medical journals.

Such a bureau as I have envisaged would entail on the part of its director a knowledge of the services of the various countries which need doctors and of the conditions in them, and he would therefore have to be prepared to visit them to assess what is needed, and to discuss their requirements with ministries of health. I feel that it would be of considerable interest to have the views of your readers on these matters to which I have referred in very general terms only. It is unfortunate to have to listen to descriptions of British medicine and training methods as old-fashioned and out of date, but for this British medicine has only itself to blame.—I am, etc.,

London E.C.3. HUGH B. L. RUSSELL.

Homotransplantation of the Kidney

SIR,—In your leading article on kidney transplantation (October 1, p. 1001), you refer to my preliminary results using 6-mercaptopurine in renal homotransplantation in dogs.[1] You state that the dogs were treated with 6-mercaptopurine before transplantation of the kidney. The drug was in fact usually started on the day that renal transplantation was performed, and the best results were obtained starting with a large daily dose which was lowered after a few days. This would be in sympathy with the view that 6-mercaptopurine is effective when administered during the inductive phase of antibody production.[2]—I am, etc.,

Peter Bent Brigham Hospital, Boston, Mass. R. Y. CALNE.

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[1] Calne, R. Y., *Lancet*, 1960, **1**, 417.
[2] Sterzl, J., *Nature (Lond.)*, 1960, **185**, 256.

Megimated Barbiturates

SIR,—The informative memorandum of Drs. B. W. McGuinness and F. J. Roberts (October 1, p. 996) on this subject, followed by the letter of Dr. C. P. Hellon (October 15, p. 1158), underlines the need for caution in prescribing members of the barbiturate group of drugs. While the best solution to the problem of accidental or suicidal overdose is, as Drs. McGuinness and Roberts point out, to stop using barbiturates altogether, this is not as yet a practical measure. For nightly hypnosis, however, satisfactory alternatives are available. Dichloralphenazone ("welldorm") gr. 20 nightly, and thalidomide ("distaval") 50–100 mg. nightly, have

proved completely satisfactory for home and hospital use and are, in our opinion, much to be preferred for routine sedation and should completely supersede barbiturates for this purpose. The wide margin of safety of thalidomide in particular, as reported by De Souza[1] and Burley,[2] is a further recommendation of its use.—We are, etc.,

T. N. Rudd.
R. N. Greenhalgh.

Southampton General Hospital.

References

1 De Souza, L. P., *Brit. med. J.*, 1959, **2**, 635.
2 Burley, D. M., *Med. Wld (London)*, 1960, **93**, 26.

Paediatric Prescribing

Sir,—It was truly a delight to read Mr. R. C. Taylor's letter headed "Infants and the March of Medical Science" (August 20, p. 599). In a succinct manner larded with humour, he has pointed out that, even in so authoritative a work as the *National Formulary*, almost no attention is paid to the prescription of drugs for infants and children. I would go further and state that, even in most textbooks of paediatrics, the subject of drugs and dosage tends to be glossed over, the authors apparently being chary about committing themselves in this manner. As a result practitioners tend to limit the numbers of drugs they use and depend on some rule-of-thumb formula to arrive at a suitable dosage.

In order to fill what I thought was a serious gap in the paediatric literature, I felt compelled to collect together all the information available on drugs and dosage in paediatric practice. As the names of many drugs are better known in the form of "concoctions made by one of those unmentionable proprietary manufacturers" I have given these equal prominence with those which are sanctioned in the name of officialdom. The result is my book *The Paediatric Prescriber*,[1] which I hope will answer the anguished but unspoken prayer of practitioners such as Dr. Taylor.—I am, etc.,

Pincus Catzel.

Klerksdorp, South Africa.

Reference

1 Catzel, P., *The Paediatric Prescriber*, 1959. Blackwell Scientific Publications, Oxford.

POINTS FROM LETTERS

Awareness and Imagination

Mr. H. W. Heckstall-Smith (Totnes, Devon) writes: Dr. S. L. Simpson (September 10, p. 806) asks if doctors may "too easily ignore patients' complaints as neurotic irrelevancies" and Dr. P. H. Addison points out just above how sad it is for surgeons to find they have operated on the wrong limb or digit. May a patient comment? The great thing seems to be that the patient as a person should make touch with the doctor as a person. It is just as disastrous for the patient to see the doctor as a mere curing-machine as it is for the doctor to see the patient as a mere case.

Sewage in the Sea

Dr. James F. Brailsford (Birmingham 15) writes: As special investigator to the late Sir John Robertson, medical officer of health to the City in 1910, I carried out a bacteriological examination of mussels sent into the City, and found typhoid bacilli in some. At this time I visited a popular seaside resort, where I found the human excreta so thick on the sands that it was impossible to walk without foully soiling my shoes. It looked as if the whole town had used the sands for squatting.

Obituary

M. DU BOIS FERGUSON, O.B.E., M.D., D.P.H.

Dr. M. du Bois Ferguson, formerly senior physician to the York County Hospital, died suddenly at Studland Bay, Dorset, at the age of 79.

Montgomery du Bois Ferguson was born on November 29, 1881, and was educated at Aldenham School and Trinity College, Dublin, graduating M.B., B.Ch. in 1905. He was resident student at Sir Patrick Dun's Hospital, Dublin, and external maternity assistant at the Rotunda Hospital, where he took the L.M. Later he was senior house-surgeon at the Borough Hospital, Bootle. After proceeding M.D. he took the D.P.H. of Dublin in 1907.

He came to York first to join the medical staff of Rowntree & Co. Ltd., then went into general practice, soon becoming assistant physician at the County Hospital, York. He did valuable service in the R.A.M.C. during the first world war, being mentioned in dispatches and appointed O.B.E. For some years before his retirement in 1939 he was the senior physician at the County Hospital. He was chairman of the York Division of the B.M.A. in 1933–4, and he was a past-president of the York Medical Society.

D. R. C. writes: The medical staff of the York County Hospital regretted that Dr. Ferguson retired comparatively early. He was an outstanding member, a man of the highest principles, with a very shrewd clinical sense. No one could be more transparently honest in deed or thought than he was, and no one could have given more help to colleagues: he was more concerned about their welfare than his own. After his retirement he was in poor health for a year or two, but to the joy of his family and friends he made an excellent recovery. His last two years were serene and contented, and his sudden end was deservedly without pain or suffering. Those of the hospital staff who worked with him will always think of him with respect and affection.

P. R. BOLUS, O.B.E., M.B.

Dr. P. R. Bolus, formerly Director of Medical Services, at the Ministry of Pensions, died in Victoria, British Columbia, on September 17. He was 80 years of age.

Percy Reginald Bolus was born on April 24, 1880, and was educated at Bancroft School and Guy's Hospital, to which he won a senior arts scholarship. Later he was awarded the Wooldridge Memorial prize, and when he graduated M.B. in 1903 he won a gold medal. After working as assistant demonstrator of histology at Guy's he held the posts of house-surgeon and registrar at the Seamen's Hospital, Greenwich. Later he was elected to the staff of the Royal Albert Hospital as assistant surgeon. Joining the Colonial Medical Service, he was posted to the Falkland Islands, where he met his wife. During the first world war he served as a major in the R.A.M.C.

In 1921 he joined the staff of the Ministry of Pensions, and the rest of his career was spent in the service of that Ministry.

J. P. T. M. writes: The passing of Dr. Percy Reginald Bolus at the age of 80 closes a loyal, active, and adventurous career, which in a man of less fortitude and resolution would have been marred by coronary disease. After five years with the Ministry of Pensions, in view of his clinical and administrative ability, he was drafted to Ottawa as the Ministry's medical representative for Canada. After an eminently successful tour of duty there of nine years he returned to London headquarters, and was appointed O.B.E. At the outbreak of the second world war he was evacuated with his department to Norcross, near Blackpool, with the rank of Director of Medical Services. There his penetrating, logical mind and clinical acumen were of the greatest value to the State and to disabled ex-Servicemen, his chief

ambition being that justice should be done. In 1942 he almost succumbed to a grave coronary thrombosis which left an aftermath of severe angina pectoris. Despite this painful handicap, he relentlessly pursued his duties, sedentary and travelling, frequently distressing his solicitous colleagues by the strenuous walking exercise in which he indulged in all weathers at Norcross until 1948, when he took up part-time pensions work in the South-west London region. In 1953, with his wife, he joined his children—two daughters and a son—and their families in Canada.

Dr. Bolus will be long remembered by his colleagues and many friends in Great Britain and in the Commonwealth for his cultured personality, unselfish devotion to duty, invincible resolution, and quiet undemonstrative endurance.

J. T. JOHNSON, D.S.O., M.D., D.P.H.

Colonel J. T. Johnson, who had a distinguished career in the R.A.M.C. and was also for some years in practice at Guildford, died after a short illness on October 5 at Wooler, Northumberland. He was 82 years of age.

John Tyrer Johnson was born at Newcastle upon Tyne on June 4, 1878. He studied medicine at the University of Durham, graduating M.B., B.S., with honours, in 1899, at the age of 21. Immediately volunteering to go out to South Africa, he served in the war there from 1900 to 1902 and then obtained a permanent commission in the R.A.M.C. He saw active service in Korea in 1903 and during the Boxer Rebellion in China. Having proceeded M.D. in 1903, he won further distinctions at the University of Durham, taking the D.P.H., with honours, in 1909, and winning the Luke Armstrong scholarship in comparative pathology.

During the first world war he was awarded the D.S.O. in Gallipoli, where he was deputy assistant director of hygiene. He was also awarded the Serbian Order of St. Sava. After the war he became successively A.D.H. at Aldershot, A.D.M.S. Meerut District, senior medical officer at Gibraltar, and finally D.D.M.S., Egypt and Palestine Command, before retiring with the rank of colonel in 1933.

After a voyage as a ship surgeon to New Zealand he went into general practice in Guildford, and later became deputy medical officer of health, with special responsibility for the casualty services, under the Guildford borough council, just before the outbreak of the second world war. Shortly after the war started he rejoined the R.A.M.C. and served throughout hostilities as senior medical officer at the Royal Arsenal, Woolwich. For some years after the war he was chairman of pensions appeals tribunals, and travelled all over the British Isles.

For the past ten years he had been enjoying a happy retirement in Scotland, and returned to his native Northumberland only a few weeks before he died. Colonel Tyrer Johnson was twice married, and he is survived by his second wife, Margaret, and by the daughter of his first marriage.

S. C. ALCOCK, M.B., Ch.B.

Dr. S. C. Alcock, who after 37 years in Reading ceased practice only a few months ago, died in hospital on October 11. He was 63 years of age.

Stanley Charles Alcock was born in Derby on March 9, 1897. His medical education at Edinburgh University was interrupted by the first world war, during which he served as a captain in the Argyll and Sutherland Highlanders. After the war he returned to the University and graduated M.B., Ch.B. in 1921. While at Edinburgh he played cricket and football for the University, and in addition he was a good golfer with a very low handicap. After holding several resident hospital posts he came to Reading in 1923, joining a partnership which developed into one of the largest practices in the town. His private practice spread over a wide area. He was devoted to his work, and many of his patients became lifelong friends. He seemed never to tire, never to be in a hurry, and was always kind and sympathetic. Though his work left him little spare time he continued his interest in games. For many years he was medical officer to the Reading Football Club, as well as being one of its directors, and he managed to play a round of golf occasionally. Chairman of the Reading Division of the B.M.A. in 1943–4, he had been honorary secretary of it from 1939 and had attended several Annual Meetings as a Representative. He was also honorary secretary of the local medical war committee from 1939 to 1944. A member of the Reading Executive Council from its inception, he was chairman of the National Service medical boards and of the Reading obstetric committee. He was also actively concerned with local charity work.

In 1922 he married Annie Nicolson, of Edinburgh, who with two sons survives him. Their sorrow is shared by a very great number of patients and friends.—F. H. A. W.

W. R. GARDNER, D.S.O., M.B., Ch.B.

Dr. W. R. Gardner, who was in practice at Brierley, near Barnsley, died in hospital on September 17, aged 71.

William Ross Gardner was born on April 1, 1889, and educated at Falkirk High School, Stirlingshire. He studied medicine at the University of Edinburgh, graduating M.B., Ch.B. in 1912 and later holding the post of house-surgeon at Lowestoft General Hospital. At the outbreak of the first world war he was a member of the Officers Training Corps, and as a captain in the R.A.M.C. he crossed immediately to France, serving first in stationary hospitals, then in motor convoys, and finally as a lieutenant-colonel in command of 138 Field Ambulance. Towards the end of the war he saw service in Italy in the Piave region, and on his return home he worked for some time with the military establishment in Edinburgh. Mentioned in dispatches three times, he was awarded the D.S.O. and bar and the French Croix de Guerre.

In 1921 he took up residence at Brierley and quickly became very busily occupied in an extensive general practice. From 1921 to 1947 he was medical officer of health of Hemsworth rural district and medical superintendent of the Brierley isolation hospital. After the National Health Service came into being the Brierley isolation hospital was renamed the Burntwood Hospital, and Dr. Gardner retained his appointment as medical officer there until his death. In 1941 he was chairman of the Barnsley Division of the B.M.A., and for a year or two he represented the Division at Annual Meetings. He was also a member of the B.M.A.'s Public Health Committee in 1943 and 1944.

A man of exceptional clinical and diagnostic skill, Dr. Gardner was beloved by his patients, and his passing has caused deep sorrow throughout the district in which he practised. He leaves a widow, a son, and two daughters, to whom deep sympathy is extended.

R. S. G. DAVIES, M.B., Ch.B.

Dr. R. S. G. Davies, who was in general practice in the Fishguard area of Pembrokeshire, died suddenly at Withybush Hospital, Haverfordwest, on October 2. He was 39 years of age.

Rowland Selby Gwyn Davies was born on May 14, 1921, and educated at the Fishguard County School and Churcher's College, Petersfield. Winning a Kitchener Scholarship, he went on to the University of Bristol, where he graduated M.B., Ch.B. in 1948. He became president of the University Students' Union at Bristol, and after graduation undertook the duties of casualty officer at the Bristol Royal Infirmary before settling down in practice in his home county of Pembrokeshire. As well as being in general practice in the Fishguard area, he became Admiralty surgeon at the Royal Naval Armament Depot, Trecwn, medical officer for West Wales to the British Transport Commission, and medical officer to the

South Wales Electricity Board in the Fishguard area. Dr. Davies was a keen yachtsman and a member of the Fishguard Bay Yacht Club. A great music-lover, he was also an accomplished pianist.

G. R. D. writes: The calamitous and unexpected death of Rowland Davies has left his patients, colleagues, and close friends stunned. On the night before he was so cruelly struck down he had happily entertained some of his close friends. We visited his flat the day he died, and where his personality was all-pervading. The grand piano lay open, the Brahms and Mendelssohn disks had not yet been replaced in their dust covers, John Donne's poems had not found their way back to the shelf where they had kept company with a vast array of books on the arts, last week's expert photographs which he had earlier developed and enlarged lay on his chair. In the next room the rough clay model of a friend's head awaited his skilled touch. Over the rain-drenched misty hills his yacht *Pamela* lay at her moorings. Such a full life ended; such talent lost.

No doctor was better loved. He was friend, counsellor, and physician. No man asked for his help in vain. Forgiving by nature, he found good in all humanity. To his friends he offered abundant warm hospitality. Conversation in his presence was witty, enlightening, and often soul-searching. He gave us loyalty unswerving, and his capacity for kindness and understanding, the repeated instances of his prolonged psychological and financial support of friends and patients, revealed us, his dearest friends, as far lesser mortals. In a short life no man brought more pleasure into so many other lives.

All bemoan his loss. People's love for him is simply understood, for as we left his flat we removed the slip of paper pinned above his consulting-room desk. On it, and portraying the man as he lived, were A. A. Proctor's words: "Judge not the workings of his mind, nor of his heart thou canst not see; for what to thine dim eyes may seem a stain, may in God's purer light be but a scar won on some far-flung battle field where thou wouldst but faint and yield."

Such was our colleague. He raised our profession's status high in the esteem of his patients, and medicine can ill afford his loss. We shall hold him in proud memory. Our wounds may heal, but our scars we shall always carry.

S. A. D. MONTGOMERY, M.B., B.Ch.

Dr. S. A. D. Montgomery, who practised first in Cleethorpes and then in Bournemouth, died suddenly on February 27, 1960, at his home in Highcliffe-on-Sea, Hampshire.

Samuel Alexander Delmege Montgomery, the youngest of thirteen children, was born on March 2, 1887. His family was long connected with Omagh, Co. Tyrone. Educated at Omagh Academy, and at Queen's University, Belfast, he graduated M.B., B.Ch. just after the outbreak of the first world war. Serving in the R.A.M.C. from 1915 to 1918, he was medical officer to the 10th Battalion of the Royal West Kent Regiment in France, where he was wounded, and later served in Salonika. After demobilization he married and settled in Cleethorpes, where he built up a reputation as a first-class family doctor, greatly beloved by his patients, and where his four children were born. In 1929 he served for a year as Chairman of the North Lincolnshire Division of the B.M.A. After his first wife's untimely death, he later remarried and moved in the early nineteen-thirties to Bournemouth, where he practised for another 15 or so years, and was active in air-raid precautions work during the second world war.

Something of an individualist, with the high ideals of the best kind of family practitioner of his generation and little love for regimentation, Dr. Montgomery found some features of post-1948 practice irksome, and presently took himself to a happy retirement with his wife at Highcliffe, where he continued to give pleasure to old friends and new until his sudden and unexpected death. He is survived by his widow and a family with strong medical connexions. His eldest son, Desmond, was killed in a car accident in 1955 while a medical officer in Aden. His youngest son is also a doctor, and his daughter married to a practitioner in Shropshire.

J. McF. writes: Sam Montgomery's passing was a great shock to me. We entered medical school together. We corresponded over the last 40 years, and I had a long letter from him just two months before his death. All his life Sam was a student of English literature; he read widely and in his younger days was a frequent contributor to the *Tyrone Constitution*. He had a keen sense of humour, was a good conversationalist, and was very popular with his fellow students. He played hockey for the university, and golf when he had the opportunity. I shall always remember Sam with affection and feel that with his passing I have lost a faithful, trusted, and valued friend.

T. S. H. writes: With "Monty" passed one of my medical heroes. When as a very raw beginner I went to his practice in 1925 as the first assistant he had ever had, there began a friendship which continued warm and active until his death this year. Save for the second world war, we saw one another often and corresponded regularly. In 1937, with two of his children, he visited Belfast with me for the B.M.A. Annual Meeting. He was always a family man with a sympathetic and affectionate personality which endeared him to people of all ages. In Belfast we stayed with my mother, and it was characteristic that he continued to write to her regularly till her death in 1951. Though circumstances limited our work together to less than two years, Monty taught me more, and had far more influence on my medical life, than any doctor before or since; and his warm friendship and that of his wife at their Highcliffe home was extended to my wife and children. He was always a good and gallant and generous friend to me and to many who will miss his genial and gentle humour and enthusiasms. May he rest in peace, and, as they say in our native Ireland, "May God be good to him."

A. A. WATERMAN, M.R.C.S., L.R.C.P.

Dr. A. A. Waterman, who was in general practice in Tooting, died at St. James's Hospital, Balham, on September 22 after a short illness. He was 42 years of age.

Arnold Aubrey Waterman was born in Trinidad, British West Indies, on May 23, 1918. He graduated B.A. at Cambridge in 1941, and later studied medicine at Guy's Hospital, qualifying in 1951. After holding hospital posts in London, he was appointed a medical officer in the Trinidad Government Medical Service. He returned to London three years ago.

D. McW. writes: Aubrey Waterman's untimely death will be mourned by very many patients, friends, and former colleagues. In the few months since he had taken over the Tooting practice he had gained a reputation for wisdom, conscientiousness, and unfailing kindness. This large but very gentle West Indian was greatly liked wherever he went, but perhaps those who were closely associated with him at the National Temperance Hospital, where he served for a number of years as house officer, R.M.O., and later as medical registrar, had the privilege of knowing him best. He never sought popularity, but seldom failed to make friends. Though angered by slapdash methods, he was tolerant with inexperience, and many an anxious houseman had cause to be grateful when his patience and robust sense of humour averted impending crisis. Medicine and music were the absorbing interests of his life, and his fine collection of records and superb instruments of sound-reproduction provided many hours of delight for his friends. His widow has the sympathy of all who knew Aubrey Waterman, and the gratitude of many who enjoyed informal evenings of opera and anecdote at their home.

MELANIE KLEIN

Dr. Dugmore Hunter writes: I should like to add a postscript to Dr. Winnicott's warm appreciation of Melanie Klein (October 1, p. 1026), and to mention in particular her work during the past decade. In these last years Melanie Klein gave much thought to problems of character formation and to the role of envy in human affairs—its destructiveness and the defences set up against it, especially the splitting mechanisms underlying schizoid thinking and behaviour, and the inhibition of creative activity induced by these defences. Her book *Envy and Gratitude* was published in 1957. She was also able to complete the long task of editing her *Narrative of a Child Analysis*, an extremely detailed account of four months' analytic work with a 10-year-old boy, but she did not live to see it emerge from the press. One of her last great pleasures was to accept an invitation from the Institute of the Pennsylvania Hospital, Philadelphia, to spend a week in residence there, giving seminars, "to further the understanding of psychotherapy with psychotic patients." This last engagement could not be fulfilled.

J. M. MUNRO KERR, M.D., F.R.F.P.S., F.R.C.O.G.

The obituary of Professor J. M. Munro Kerr was published in the *Journal* of October 15 (p. 1166).

Professor G. I. Strachan writes: The passing of Professor Munro Kerr at the advanced age of 91 seems almost like the end of an obstetrical era. In long retirement, far from his native Glasgow, he was only a name to the more junior of our colleagues, but in his heyday he was a power in the land and a man of international reputation. Although his chief monument is his classic *Operative Midwifery*, later *Operative Obstetrics*, he wrote extensively on practically every aspect of obstetrics and he adorned every subject that he discussed.

He kept himself well abreast of modern developments in obstetrics such as soft-tissue placentography, *x*-ray pelvimetry, and the investigation of pregnancy toxaemia, but he was essentially a clinician, and those of us who were privileged to work with him in his earlier days were continually impressed by his remarkable clinical judgment and skill. He was one of a generation of pioneers which included Blair Bell, Berkeley, Bonney, Fothergill, and Donald, and it is hardly to be expected that we shall see their like again. Now that his tall, slim, immaculate personality has faded into the shadows, his memory will remain dear to those of us who knew him, and especially to those who worked with him.

J. C. M. writes from Georgetown, British Guiana: It is with great sorrow that I learn of the death of Munro Kerr. To those of us who were privileged to know him and to collaborate with him his loss is much more than the breaking of a link with the past, for he was a wise and kindly counsellor, and a friend who radiated good humour and inspired confidence for the future. To a younger generation of obstetricians it may come as a surprise to learn that this almost legendary figure was, till so recently, still with us. His influence on obstetrics extended over the greater part of a century. It was in the industrial Glasgow of the late eighteen-hundreds—a city where malnutrition and rachitic deformities were rife—that he had his training in the rough and tumble of obstetrics. Then, too, he witnessed some of the desperate caesarean operations that were beginning to be performed. This experience caused him to devote himself to means of perfecting the operation; and his introduction of the "lower-segment" technique was in large measure responsible for the present-day safety of the operation. In this and in many other matters he was an innovator and—perhaps even more important—an untiring evangelist.

Munro Kerr was one of the most widely read medical men of his time. English, French, and German publications were all taken in his stride, and, almost to a fault, he followed, especially as he grew older, the work of his younger colleagues, never hesitating to divest himself of old ideas if these should be proved untenable or based on doubtful evidence.

Though a good bedside teacher, he was not a fluent speaker. His great strength lay in the charm of his writing—and this was apparent whether in a personal letter or an erudite textbook. In each there was the same simple but arresting phraseology, the shrewdness of argument, and the occasional upsurge of pawky Scots humour which endeared him to the reader. But with all this appearance of spontaneity, there was hard work too. "Writing is fun," I have heard him exclaim, "there is great satisfaction in pondering for a whole day and then selecting the right word for the difficult phrase."

When infirmity made it more and more difficult for him to leave Canterbury—his chosen home of retirement—and visits to the London libraries were no longer possible, he turned to the writing of historical sketches. He was particularly gratified when, in his 87th year, he was asked to give an address to his old university. This he did, choosing very appropriately for the Glasgow school the life and work of John Hunter.

And still the urge to write continued. In a letter I received only a few months ago he announced that he was engaged on something new, *The Reminiscences of a Victorian Gentleman*. The Victorian Gentleman is now, alas, departed, but the influence of the Grand Old Man of Obstetrics will long remain.

Dr. W. G. Mackay writes: I was blessed with the great good fortune to be Professor Munro Kerr's Hall Fellow during the period he occupied the Regius Chair of Midwifery at Glasgow University. In these times Glasgow was the hub of the obstetrical universe and J. M. M. K. the undisputed world authority in his specialty. Every relevant article which was published quoted his writings, and from all quarters of the globe came obstetricians both great and unknown to pay respects and homage to the acknowledged master and see him at work. His was a name to conjure with, especially where the candidature of professorial chairs or other sought-after posts was at stake. These were halcyon days for the Glasgow school of obstetrics.

But to myself, and I think to all who knew him, the glamour of Munro Kerr was not a reflection of his fame and achievements, gigantic as these were—it radiated from a beautiful personality. No man was more lovable or more loving. He possessed by nature and by grace all the attributes of a perfect gentleman. Tall, dark, and slender, very good-looking, patrician and thoroughbred, always immaculately dressed and groomed, with impeccable manners and courtesy, he stood out as distinguished and imposing at any gathering at home or abroad, and was usually placed in, and always adorned, the seat of honour. He clung to one or two of the marks of an Edwardian dandy—the monocle, for instance. In conversation his wise face lighted up and became transparent with understanding and recognition to an extraordinary degree, and in addressing an audience it was not unusual for him to get carried away, his enthusiasm for his subject reaching a white heat. Pervading this imposing presence was an aura of merriment and festivity: his humour was never long in bubbling to the surface.

He treated his assistants as if they had been his own sons, and to them he was a second father, almost a second god. Once adopted they were not only "with" him they were "of" him, sharing everything and left out of nothing. They could depend upon him utterly and absolutely. Nonentities they might be, but he regarded them as equals: they became collaborators and co-authors in his multitudinous papers and books, they were introduced with parental pride to the great men of the profession, they lunched with the professor at his club. In the evenings they got a warm welcome to his sanctum at the back of his house, where, ensconced among books, he was

interminably writing. Not least in the estimation of a young man was the delight, at the tea interlude, of ascending to the drawing-room and finding if lucky one of his beautiful daughters at home in addition to his charming, gentle, and gracious wife. Failing this, the libations would be stronger, and Munro Kerr would recount all the wisdom of the universe until the small hours.

J. M. M. K. was modest about his achievements, but he told one story with pardonable pride. As a very young obstetrician he read his first paper at the Edinburgh Obstetrical Society in which he advocated the use of caesarean section in opposition to difficult forceps delivery in cases of contracted pelvis. In the subsequent discussion a very senior and eminent Edinburgh obstetrician got up and said he had never come across a case in which he could not pull the head through the pelvis with forceps. To this Munro Kerr replied that he was not quite so strong. Time vindicated this and most of the innovations which he sponsored, for he emblazoned the whole realm of obstetrics with the motto, "Non vi sed arte."

Munro Kerr shared with artists and poets the priceless faculty of seeing the world through rose-coloured spectacles, of seeing a pebble as a gem and a toad as a swan. The number of people he held in the highest esteem, if not actually setting them up on pedestals, was legion. Where other men might tend to belittle or depreciate he was more likely to canonize. He seemed to live in a scintillating and exhilarating world in which heroes and demi-gods were in a comfortable majority. A monster for work, he engaged in it with zest as if it were the most engrossing and fascinating hobby ever planned by the Almighty for the delectation of man. He would exhort his younger colleagues to "hold up the torch of high endeavour" and to do whatever they undertook with all their might and main, but his own example was the greatest inspiration.

In his old age, when he had laid down his tools, I said to him he must have a wonderful feeling of fulfilment. He replied that the tragedy of existence was that one could accomplish so little in the span of a lifetime. One is grateful that the world can produce such men, even if only at rare intervals.

G. H. THOMSON, M.B., Ch.B.

The obituary of Dr. G. H. Thomson was published in the *Journal* of October 15 (p. 1167).

N. C. F. M. writes: I wish to add a personal tribute to the late Dr. G. H. Thomson, who practised in Longtown, Cumberland, for the past 32 years: for 10 years of that period I was associated with him as his assistant. He was a man of high ideals, who always gave of his best. He shunned and positively abhorred cheap popularity. To him the truth was always more important than the opportunity to gain temporary favour. His standard of practice was of the highest, and his efficiency in running it filled me with great admiration and envy. His organizing ability in spheres outside the practice of medicine was amazing. Any job he took up had to be done well, and there were never any half measures. He did a great deal for Longtown outside his professional duties, and his striving to attain the peak of knowledge and efficiency in this work was first-class. He would read and study everything and anything about the subject to equip himself fully for the task.

It was natural that, as his assistant, I fell far short of his high standard. For this he always made most generous allowances; and if it proved necessary he would show the utmost loyalty and back me to the limit should I ever make a mistake. I learned a great deal from him and benefited enormously from his example and experience. He had little time or patience for those people who tried to be clever, and he got really annoyed with anyone who tried to cover up deficiencies, and especially lies, by trying to influence him with honeyed words. His personality was such that he could be most controversial. This kept you on your toes, but he invariably, if wrong, graciously conceded any point in the most charming manner. He never wore his heart on his sleeve, and could be austere and impatient: this did not, however, blind him to the weaknesses in others, and he could approach them with understanding, kindness, and consideration.

His main fault lay in always being shy of his greatest attributes. He almost seemed to put up a barrier to conceal them, which was a great pity, for he had high ideals and an unequalled faculty for always striving to give of his best. He always seemed rather ashamed and even annoyed to be told of them, and he was certainly the last man to admit that he had any at all. I will miss him a great deal, for my association with him reached, at times, very intimate levels, and from him I learnt the very best way to run a practice. Even our disagreements produced lessons of value, and it was most stimulating to work with and for so controversial a personality. We can indeed offer to his widow and three daughters our sincere expressions of deepest sympathy.

Sir JOHN GOODWIN, K.C.B., K.C.M.G., D.S.O.

Hon.D.Sc., F.R.C.S., Hon.F.R.C.S.Ed.

The obituary of Sir John Goodwin was published in the *Journal* of October 22 (p. 1242).

Sir HENRY BASHFORD writes: I only came to know John Goodwin, as a Wiltshire neighbour, during the last twelve years of his life, but nobody could have doubted, almost at first sight, the reason for his laurels, both as Director of Medical Services in the latter years of the 1914–18 war and afterwards as a Governor in Australia. During most of his last years, the upkeep of a country house having become too burdensome, he lived in a hotel in Marlborough, where he had a small private sitting-room. But even in his late seventies and early eighties he was still a tall and upright figure and an ardent shot and fisherman, who loved to help an occasional boy from the College to beguile a trout from the Kennet or give a tip or two on the ways of a hare to the young followers of the newly formed College beagles.

Reminiscing, as old men will, he was always more ready to talk about sport than professional matters, but he did once tell me, with a twinkle in his eye, of his coaching at Buckingham Palace before taking up his governorship. "You mustn't forget," King George V said, "that you will be my personal representative out there, and if any of my sons visit you, as they may well do, mind you see that they treat you with proper respect." The King then asked him what his own politics were. Goodwin, however, in spite of his natural simplicity and forthrightness, was not to be drawn, even by his Sovereign, for whom he had the deepest admiration. 'But I can promise you this, Sir," he said, "that nobody in Australia will know either."

Although towards the end he became very deaf and nearly blind, his sense of fun never forsook him, and one of his favourite stories was about an old lady, a fellow occupant of the hotel, who once invaded his sanctum. On the wall above the fireplace was a row of four mounted fox masks. Each of them was the emblem of a never-to-be-forgotten day, and one of these had left him, in a winter dusk, more than eighteen miles from home, most of which he had had to (or did) walk in order to spare a tired horse. "And do you mean to tell me, Sir John," the old lady inquired, "that you actually shot all those?"

Mrs. Eleanor Elizabeth Lloyd died on October 20 at Hartley Wintney, Hampshire, on the eve of her 106th birthday. A grand-niece of Sir Charles Hastings, she was the last surviving link with the founder of the British Medical Association. Though it is 94 years since Sir Charles Hastings died, Mrs. Lloyd remembered him well, for as a girl she used to pay him a regular visit at Worcester on New Year's Day.

Medical Notes in Parliament

PORTENTS OF THE NEW SESSION

[From our Parliamentary Correspondent]

Sufficient indications have emerged from the parade of Ministers at the Conservative Party Conference to show that in home affairs the second session of this Parliament will be largely occupied in continuing efforts towards social reform. The Queen's speech at the ceremonial opening on November 1 will name most of them, and set the pattern of intended action; but Ministers have already let fall enough evidence of their several purposes to enable the general prospect to be seen.

Reform of the Criminal

An outstanding measure will be a new Criminal Justice Bill. Its outlines remain vague pending the reports of advisory bodies on the police, corporal punishment, and approved schools, all of which are expected within the next few weeks. Its underlying motive, however, is clear from Mr. R. A. Butler's phrase, "As long as I am Home Secretary I intend to continue with the tradition to persist with reform." This appears as a direct answer to those, inside the party and outside, who would deflect policy from reform of the criminal to the prevention and punishment of crime. Such limited statement of aims as was added to this by Mr. D. Vosper, Under-Secretary at the Home Office, was described as a constant search for the right penalties—something that would protect the public, deter the potential offender, and reform the criminal. He deliberately withheld comment on the reintroduction of corporal punishment because of the imminent publication of the committee's report, saying only that whether corporal punishment should be introduced among the positive steps to deal with the increase in crime must depend on the committee's observations.

Law on Suicide

There is more definite form for the expected legislation to modify the law on suicide, a subject to which Mr. Butler has more than once turned an attentive ear, for here the Criminal Law Revision Committee has fashioned a draft Bill as the kernel of its recommendations (see p. 1301). This, if adopted, would abolish the rule that suicide is an offence, and make the aiding, abetting, counselling, or procuring the suicide or attempted suicide of another person an indictable offence subject to a maximum penalty of 14 years' imprisonment.

"Drink and Driving"

Mr. Ernest Marples still retains his ambition as Minister of Transport to see a marked reduction in road accidents, and he hopes to see passed a Bill for which his text is "Drink and driving do not go together." He has been impressed by what has been achieved in America, where he says drinking by drivers has been stopped—"I want to do the same thing here"—and has made a close study of Scandinavian practice. Presumably he will seek his purpose through stricter regulations and some form of analytical tests of alcoholic intake among road users. We have his word for it that the new measures will have an unpopular impact when they appear but will save many lives.

Means Test for University Awards

Sir David Eccles, Minister of Education, has turned aside for the time being demands for the abolition of the parental means test for university awards, and has accepted only the minority report of the Anderson Committee that the income scales should be revised. This is to be done "without prejudice to the abolition of the means test if on fuller examination it should turn out that abolition is the best way to do the job." A radical revision is promised soon, and will begin to operate next autumn.

Mr. Enoch Powell

Mr. Enoch Powell, now Minister of Health, was among the familiar figures who appeared in a new role on the conference platform. He was brought into the record by the luck of the draw, a resolution chosen by ballot for the final session, which deplored the injustice of medical services being available without charge to foreign visitors from countries without reciprocal arrangements for British tourists while British residents were denied as private patients the benefit of Health Service prescriptions. While he did not refuse "good Samaritan" treatment to the stricken visitor, and looked hopefully towards the extension of reciprocal arrangements for treatment, Mr. Powell took the motion as an encouragement to see what more might be possible to prevent abuse. This implication of tighter administration will be noted with interest by those who regard Mr. Powell as being in financial matters on the prudent side of orthodoxy, and they will no doubt reflect that his tenure at the Ministry of Health began early enough for his influence to be felt in the preparation of the next estimates.

Medico-Legal

PARENTAL CONSENT TO TREATMENT

[From our Legal Correspondent]

In March this year the Sheffield Regional Hospital Board approved a plan to set up juvenile courts in hospitals if parents refused to permit an operation on their child which seemed urgently necessary (*Journal*, March 26, p. 943). This plan has been adopted in Cambridgeshire, and has now been put into effect for the first time, it is believed, at the Millroad Maternity Hospital, Cambridge (*Yorkshire Post*, October 21).

On October 19 a rhesus-positive baby was born to a Newmarket couple. The father, a Jehovah's Witness, refused on religious grounds to allow a blood transfusion to be performed. A juvenile court was convened under the chairmanship of Lady Rothschild at the hospital on October 20. The county child-welfare officer applied for custody of the baby under a "fit persons order" on the ground of wilful neglect in a manner likely to cause unnecessary suffering. Dr. Janet Bóttomley and Dr. Robert Prosser were called to give evidence of the probable ill consequences of failure to perform the transfusion. The father gave evidence of his religious objections, and called a Jehovah's Witness minister in support of his case. The court granted the order, and the transfusion was performed.

Although an appeal will serve no practical purpose as far as the father is concerned, he may well appeal for the purpose of obtaining a direction from a superior court for future cases.

THE "MUMMY" CASE

[From our Legal Correspondent]

On October 18, at Denbighshire Assizes, Mrs. Sarah Jane Harvey, aged 65, widow, of West Kinmel Street, Rhyl, was found not guilty of the murder of Mrs. Frances Alice Knight in 1940 (*The Times*, October 19). Mrs. Harvey, however, pleaded guilty to two charges of obtaining sums of £2 on dates in May, 1940, and April, 1960, by falsely pretending that Mrs. Knight was alive.

In a statement to the police on May 6, Mrs. Harvey stated that Mrs. Knight came to live with her in 1940. Mrs. Knight's husband was paying her £2 per week under a maintenance order, the money being paid through a court officer. Mrs. Knight was virtually a cripple and for that

reason gave Mrs. Harvey a written authority to draw the money for her very soon after going to live with Mrs. Harvey. Mrs. Harvey's statement continued by stating that about four or five weeks after Mrs. Knight's arrival, Mrs. Harvey found her lying on the floor of her bedroom in a nightdress and coat screaming and complaining of pain: a few minutes later she died. Mrs. Harvey was "scared stiff" and pulled the body along the landing and put it in a cupboard in which she also put some flypaper: she then locked the cupboard. Mrs. Harvey told no one of the death, and "to keep things quiet" she kept going to the court office each week to collect the maintenance payments. Mrs. Harvey pleaded not guilty to the murder of Mrs. Knight.

The matter only came to light after 20 years when, at the beginning of 1960, Mrs. Harvey was admitted to hospital: her son, Leslie Harvey, in the course of redecorating the house in her absence, forced open the lock of the cupboard. As a result, the police were informed, and Dr. E. G. Evans, a Home Office pathologist, and Dr. A. Clift, biologist on the staff of the north-western forensic science laboratory at Preston, examined the cupboard and its contents on May 5.

Dr. Evans, giving evidence, said that the cupboard contained thick, black, dust-ridden cobwebs. The body lay on the floor with a foot exposed. Near the foot was an empty disinfectant bottle, and a fly-paper was hanging up in the cupboard. There were hundreds of pupa cases in the dust over the body. The abdomen, thighs, and legs were covered by a blanket-type of material, in the folds of which were two portions of fly-paper. The upper part of the body was clothed in a long-sleeved nightdress and a coat or dressing-gown. Across the neck were two portions of material.

On removing the body to the mortuary, Dr. Evans found it to be brick hard, resisting even a hammer and chisel, except on the scalp and face, where slight pitting could be obtained. There was a groove running from front to back of the neck on the left side. A hanging piece of material or tissue dropped as he touched it, but he saw another piece projecting close to the skin, and by following this with his finger into the groove he extracted a piece of material with a knot at the end of it which appeared to be a reef knot. As he laid the material on the bench, it remained in a curve: it appeared to be of stocking material. A groove round the right side of the neck was continuous with the groove on the left side.

Dr. Evans had no reason to believe that the process of mummification was anything but natural. There was no fracture of the skull, but no brain. There was insufficient tissue to be able to state on medical grounds what was the cause of death. In cross-examination Dr. Evans agreed that from case sheets of Professor Cohen (now Lord Cohen of Birkenhead) dating from 1938, it was clear that Mrs. Knight was suffering from disseminated sclerosis; he also agreed that this might cause paraplegia in flexion, which involved the drawing up of the legs to a position similar to that of the body in the cupboard, and that this condition might well cause some disorder of the throat. He was unable to state whether the ligature in this case was put on before or after death, and he agreed that where there was a neutral ligature, such as a collar, round the neck and the skin became swollen after death one would find a groove. He could not agree with the opinion of Sir Sydney Smith and Dr. Camps that the groove was caused in this case by post-mortem changes, but he did concede that a woman who had no sock available might well wrap her throat in a stocking if she had a cold or sore throat, and to be of any use it would have to be applied firmly.

Dr. Evans gave six reasons in support of the suggestion that Mrs. Knight was homicidally strangled by ligature: first, the groove round the neck; secondly, the depression on the left side of the neck; thirdly, a depression on the thyroid cartilage; fourthly, the finding of a ligature on the neck; fifthly, the fact that the ligature would be said to be tight; and sixthly, the evidence as a whole. Dr. Evans later agreed that the stocking was not twisted and the pattern was not stretched.

Dr. A. Clift gave evidence that from a stitch count and from the appearance of the stocking he formed the view that it had been stretched. He did not agree with the view of the Manchester Chamber of Commerce testing-house that the stocking had not been abnormally stretched. The only way to judge whether the material had been stretched was by counting stitches and looking at the appearance of the material.

On the final day of the trial Dr. Clift collapsed while under cross-examination. The court rose for a short while in consequence, and when the court sat again the Solicitor-General, on behalf of the Crown, withdrew the charge of murder from the jury.

Mr. Justice Davies stated that he entirely agreed with that course. Dr. Evans had been unable to say what was the cause of death, whether it was natural or unnatural, or whether the ligature had been applied before or after death. Unless the prosecution could prove that the stocking had been stretched, the prosecution case must fail. It appeared that the prosecution was in no position to prove this. Mr. Justice Davies refused a defence application for costs and proceeded to sentence Mrs. Harvey in respect of the two charges of obtaining money by false pretences. A sentence totalling 15 months' imprisonment was imposed.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on October 11 it was resolved to confer the degree of M.A. upon Sir George Lindor Brown, F.R.S., Waynflete professor of physiology in the University.

Dr. W. J. Cliff has been re-elected to the Philip Walker Studentship for 1960–1.

UNIVERSITY OF CAMBRIDGE

Lord Adrian, Master of Trinity College, has been appointed a Deputy Vice-Chancellor of the University for the academical year, 1960–1.

UNIVERSITY OF ABERDEEN

Dr. John A. Shanks has been appointed to a terminable lectureship in pathology from December 1, 1960, and Dr. Gordon A. German to a research fellowship in physiology from August 22, 1960.

Dr. I. M. Glynn has been elected into a Fellowship of Trinity College, on appointment as College assistant lecturer in physiology.

UNIVERSITY OF LONDON

The following degrees were awarded in August:

M.D.—J. A. M. Acer, G. Belyavin, D. Burman.
M.S.—I. F. K. Muir.

The following candidates have been approved at the examinations indicated:

Academic Postgraduate Diploma in Clinical Pathology.—E. C. Christian, J. L. Grech, B. K. Jha, H. J. Koornhof, H. G. McDonald, J. B. MacGillivray, Rohma Newman, W. H. Payne, M. J. Phillips, M. Qudratullah,, S. M. Sadique, J. Shapiro, I. O. K. Udeozo, K. Zahur-Ud-Din.

Academic Postgraduate Diploma in Public Health.—U. Broccolo Tommasi, W. J. E. Darling, E. D. O. Okeke, D. G. B. Singh, N. Tekirli, Joyce D. Waye, Jean B. Wickings.

External Diploma in Clinical Pathology.—Dona P. Wijesinghe.

UNIVERSITY OF BIRMINGHAM

Dr. H. G. Lambert has been appointed a temporary lecturer in the Department of Anatomy.

In Congregation on July 16 the honorary degree of D.Sc. was conferred on Sir Geoffrey Jefferson, F.R.S., Emeritus Professor of Neurosurgery in the University of Manchester.

The following degrees were also conferred on July 16:

M.D.—F. H. Kemp (with honours), J. C. Haworth.
Ch.M.—F. Ashton (*in absentia*).
Ph.D.—*In the Faculty of Medicine*: J. D. Cumming, M.B., Ch.B.
M.B.—[1]J. Herbert (with second-class honours), O. A. Adenubi, K. Arthur, Helen S. Atkin, T. C. Barker, D. M. Batty, M. Baum, Pauline J. Begley, M. C. C. Bird, I. A. O. D. Brodie, Elaine K. Broom, [2 3 4]M. J. Chamberlain, [4]B. Chance, P. J. Collis, P. J. Connop, M. J. Critchley, R. Cruthers, M. H. Daly, Gladys E. Dixon, P. M. Ellis, [1]E. F. Evans, Anne S. Fawkes, T. J. Fidler, T. R. Fisher, Marion Gillett, D. Gompertz, J. M. Goodburn, Gloria A. Griffiths, J. D. Hamer, Rosemary E. Harris, A. R. W. Harriss, L. P. Harvey, C. J. Hazledine, M. Hedden, Rosemary E. Heron,

J. A. Hickman. [2]B. D. Hill, M. K. Howard, R. C. Hughes, J. Hurst, [2]Brenda James, Cecily A. Jenkins, [4]S. A. P. Jenkins, J. M. Kay, M. J. Kestle, E. J. Knight, Jadwiga E. M. Krzysztoporska, Elisabeth D. McGuinness, R. McMurdo, J. Morley, R. D. Mumford, C. G. F. Munton, R. J. Oakey, V. B. Odunlami, D. Oldroyd, J. L. Pearsall, J. H. W. Pexman, P. H. W. Rayner, [2]D. Riddoch, A. G. Ringer, Theresa O. Scanlan, [1]C. J. Smallwood, Patricia A. M. Smith, B. Stone, J. R. Storer, Elizabeth A. Stubbs, Beryl O. D. Taylor-Lewis, J. F. Thompson, Christine C. Tong, P. J. Tovey, [5 6]B. A. Wharton, P. J. Wheeldon, Pauline Whitfield, B. Wilson A. Worrall. (The degree of Ch.B. was conferred *in absentia* by special warrant on June 20, 1960, on all the above, who now receive the degree of M.B. Dr. J. Herbert being awarded honours).

[1]Distinction in surgery. [2]Distinction in obstetrics and gynaecology. [3]Distinction in forensic medicine and toxicology. [4]Distinction in pharmacology and therapeutics. [5]Distinction in paediatrics and child health. [6]Distinction in social medicine.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on October 13, with Sir Arthur Porritt, President, in the chair, Professor Erling Dahl-Iversen, of Copenhagen, and Professor Jan F. Nuboer, of Utrecht, were elected Honorary Fellows of the College.

A resolution of condolence was passed on the death of Sir Gordon Gordon-Taylor.

Professor L. N. Pyrah was admitted to the Council, and Professor B. Cohen as Nuffield Research Professor of Dental Science.

The Handcock Prize was presented to Dr. Sonia G. Bolton, of King's College Hospital; and A. S. Coulson, of Hendon Grammar School and Queen's College, Cambridge, was admitted as the twenty-ninth Macloghlin Scholar.

Diplomas of Fellowship were granted to S. M. Cameron and Prakash Narain Tandon, and diplomas of Membership to P. B. Evans, M. T. Jones, and K. Kyei-Mensah.

Diplomas of Fellowship in the Faculty of Anaesthetists were granted to the following successful candidates:

D. Wakely, B. R. Whittard, D. S. Hutton, C. Bishop, D. C. Jackson, J. E. S. Relton, D. W. Atherley, G. J. Taylor, B. R. P. Murray, J. E. Utting, Zbigniewa A. Jordan-Sikorska, A. Maciejewski, L. J. F. X. Dunkin, A. S. McC. Lamont, J. Cox, P. B. D'Souza, Maureen E. Hardeman, K. G. Smith, R. P. Badola, M. E. H. Barrow, T. H. Howells, S. W. McGowan, C. Ward, S. J. S. Webb, Ming-Hon Yeung, J. Baldasera, F. E. Bennetts, R. A. Browne, G. H. Bush, E. R. J. Emery, Ruth Hutchinson, T. N. Munro, I. S. Paterson, H. G. Pledger, J. W. Sandison, J. P. Alexander, N. H. Doctor Sylvia L. S. Hui, J. D. Kinnell, R. N. Lewis, W. T. McNeil, D. S. Robbie G. T. Spencer, J. G. Whitwam, A. D. Crew, D. G. Larard, Audrey M. Peeling.

The following diplomas were granted, jointly with the Royal College of Physicians of London:

Diploma in Laryngology and Otology.—G. Chattopadhyay.

Diploma in Child Health.—J. E. J. Aiyathurai, W. W. Akroyd, Shahida I. Ali, I. Sha'Aibu Audu, S. J. Azzopardi, B. K. Basu, G. Beaumont, Felicity M. Bedford, K. S. R. Bedi, K. H. Belgaumkar, D. Bevan, M. D. Billington, M. S. H. Bokhari, N. R. M. Buist, G. W. Chance, T. L. Conradie, P. R. Dange, A. J. Dell, H. R. de Souza, B. L. Dodson, G. J. Ebrahim, Sundari Ebrahim, Davina C. Embleton, Eileen Evans, A. C. Fairburn, S. G. A. Forsyth, Valentine I. French, A. W. Galbraith, P. C. Garg, L. L. Ghelani, K. D. Gill, B. Ll. Griffiths, J. Grover, Indira Gupta, V. C. Harrison, W. Hazeldine, H. J. Houston, Y. E. Hsia, E. H. Innes, Kunjamma Itty, J. Jacobson, Patricia H. M. Jones, A. Ketusingha, D. Laha, P. Lanzkowsky, Stephen Leung Wing Chiu, A. R. Levin, S. R. McKay, S. Madhava Rau, H. J. Marrable, Anila Mehta, R. E. Midwinter, Janette Millar, J. D. Miller, D. J. Moorhouse, P. Morris, Y. Motala, H. Mumtaz Husain, M. F. Nasser, A. D. Noble, L. A. Nouri, Bridget O'Connell, Marjory E. Plumb, Elizabeth J. Porter, R. Prasad, Sheila G. Quain, Venkata S. Rajagopalan, A. Ramasubramanian, Susan E. M. Richards, A. P. Roberts, J. Roy, A. K. Sain, J. V. Sawdy, Theresa Sebestyen, R. N. Sen, Don C. B. Senaratne, Saida Siddiqi, D. J. Sills, P. H. Sive, G. J. A. I. Snodgrass, S. D. Stephen, S. R. Suxena, Dinar Talati, P. K. Talukdar, E. V. Tetteh-Lartey, Patricia M. S. Vaughan, P. L. Verma, Cecilia C. Ward, Gillian M. Watkins, H. A. D. Weerasooriya, R. E. Wild, J. H. Williams, G. B. Winter, Julia M. Winter, H. O. Wooller, Ma Sein Yee, Janet C. J. Young, Ka Man Carmen Yuen, Z. H. Zaidi.

Diploma in Ophthalmology.—G. N. Ahmed, S. P. Amoils, J. D. C. Anderson, J. L. Banik, J. H. Cameron, J. S. Cant, A. J. Chadwick, D. K. Chaudhari, V. M. Deval, W. N. Dugmore, F. X. Fernandez, D. P. Gale, W. G. Gaston, N. Gibbons, Florence C. Gordon, Melody J. Grice, R. M. Halley, R. H. S. Hellein, T. Hoole, Y. Husain, B. H. Irani, S. N. Kalita, J. H. Kelsey, J. B. Kelshiker, B. R. Kesby, T. Kohli, P. J. Kriel, R. Levy, W. C. Logan, J. D. C. Macdiarmid, M. B. R. Mathalone, M. B. Mehkri, J. H. Rickeard, I. R. Robertson, B. R. Sinha, E. J. Sinton, A. A. Syed, T. A. J. Thorp, Luke Shu-Ling Tsai, S. Velauthan, R. Wiss, M. Yaqin.

Diploma in Physical Medicine.—G. M. Cochrane, Joan M. Evans, Shona Hodgson, E. A. Kauffmann, Don R. D. B. Kulatunga, D. Y. Mackenzie, D. A. H. Yates.

Diploma in Tropical Medicine and Hygiene.—D. Bagchi, J. S. Bailey, H. Baquir, J. D. Barrett, P. A. Baumann, K. A. Beahan, F. E. P. Bernard, E. G. A. Bernez, J. H. Bradshaw-Smith, K. R. Dalley, M. H. Davies, F. L. Dunn, W. R. O. Eggington, W. O'C. FitzPatrick, M. A. Gaffar, F. C. Grant, J. Grant, Md. Nasirul Haque, A. J. M. Hargreaves, J. A. Hashmi, Heini M. Hinnanen, M. Houmoller-Jorgensen, R. A. Iles, F. Jatoi, Ursula Jehles, H. N. Khan, A. A. A. Khallaf, S. C. Kundu, J. W. G. McDougall, W. P. Maclay, V. M. Joglekar, N. MacLean, D. McSwiggan, Narges Mahaluxmivala, M. A. Marghoob, W. C. Moffat, J. G. Moran, S. K. Mukherjee, L. Mullins, Amarut Na Songkhla, Y. P. Narula, N. W. Nicholson, H. Noorparvar, J. W. Norris, P. L. Pearson, N. C. Pegu, M. H. Rahman, R. J. Read, M. A. Rozalla, Saif-ul-Haque, A. J. Salter, R. R. Schenck, Md Maswood Alam Shams, S. Sharan, G. G. Singh, B. B. Sinha, G. L. Smith, P. J. Stevens, A. W. Swiecicki, I. Tabibzadeh, S. B. Telford, W. Wagstaff, J. G. Winwick.

Diploma in Industrial Health.—A. K. Sen, Than Myint.

Diploma in Medical Radiodiagnosis.—G. I. Verney.

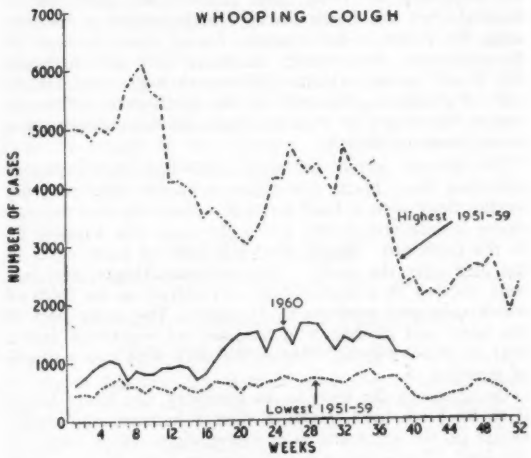
Diploma in Psychological Medicine.—G. F. Burke, A. McQuaid.

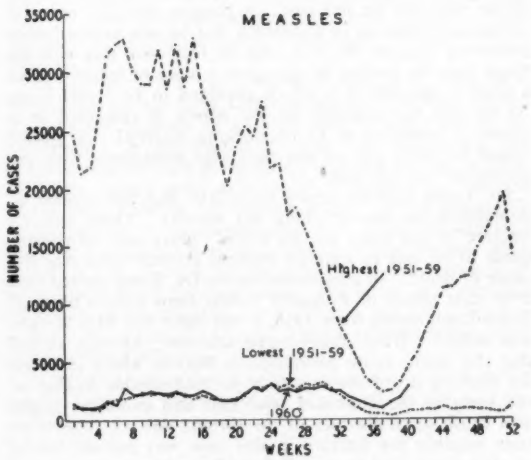
Diploma in Anaesthetics.—C. K. Davies.

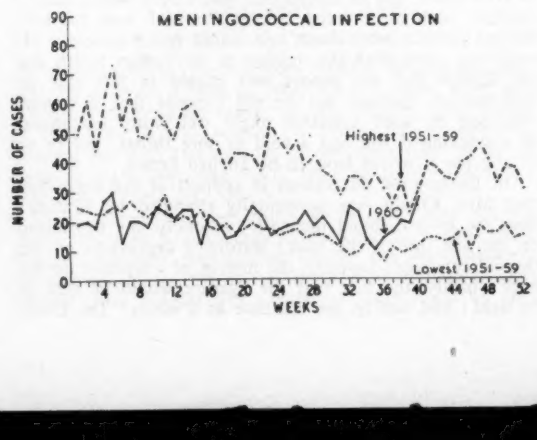
Vital Statistics

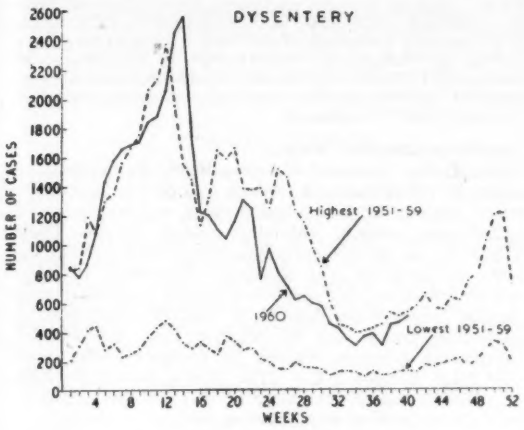
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

Measles	Week Ending Oct. 8	Oct. 15
Lancashire	934	**1072**
Burnley C.B.	86	**120**
Liverpool C.B.	82	**152**
Dysentery		
Derbyshire	1	**15**
Repton R.D.	0	**15**
Gloucestershire	9	**35**
Tetbury R.D.	0	**27**
Staffordshire	20	**13**
Newcastle under Lyme R.D.	16	**12**
Surrey	12	**45**
Epsom and Ewell M.B.	0	**32**
Yorkshire West Riding	46	**66**
Leeds C.B.	15	**28**
Doncaster R.D.	0	**10**
Glasgow	80	**144**
Food Poisoning		
Middlesex	11	**21**
Edmonton M.B.	0	**10**
Warwickshire	5	**25**
Birmingham C.B.	3	**24**
Diphtheria		
Warwickshire	0	**2**
Birmingham C.B.	0	**2**

Road Deaths in August

589 people died as a result of road accidents in August, 43 more than in August last year. This included 81 children, 4 more than a year ago.

The total number of casualties for the month was 32,976, over 1,400 more than in August, 1959. During July and August deaths of motor-cyclists fell by 15%—a reflection partly of the estimated decrease in motor-cycle traffic. The total number of deaths on the roads up to the end of August this year was 4,222, an increase of 431 over the first eight months of 1959. Child deaths were 10% more than for this period last year. The largest percentage increases of deaths for the first eight months this year were among motor-scooter riders and passengers (40%) and among drivers and passengers of other vehicles (20%). Motor traffic, as a whole, increased by 8% compared with a year ago and by 21% compared with 1958.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 8** (No. 40) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	3	0	0	0	1	1	0	2	0	1
Dysentery	500	112	148	26	7	529	48	236	6	1
Encephalitis, acute	3	2		0		3	0		0	
Enteric fever:										
Typhoid	4	1	1	2		2	1	0	1	
Paratyphoid	7	0	0	0		9	1	1(B)	0	17 (B)
Food-poisoning	225	19	26	4		230	34	16	4	
Infective enteritis or diarrhoea under 2 years				16	40				29	52
Measles*	2,853	112	71	4	9	822	36	16	16	32
Meningococcal infection	28	2	7	0		23	0	0	1	1
Ophthalmia neonatorum	16	1	3	0		16	2	10	0	
Pneumonia†	199	13	113	0	1	219	16	147	3	2
Poliomyelitis, acute:										
Paralytic	14	4	0	1	10	19	4	0	1	3
Non-paralytic	4	1	1			9	2	2		
Puerperal fever§	194	35	4	0	1	211	35	8	1	
Scarlet fever	357	31	54	32	24	869	45	127	35	40
Tuberculosis:										
Respiratory	385	53	63	9		396	41	53	12	
Non-respiratory	46	8	7	3		51	4	5	5	
Whooping-cough	1,021	90	113	5	24	485	22	90	4	71

DEATHS	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	1	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0		0	1	9	0	0	0	0
Influenza	7	0	1	0	0	7	1	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	467	38			5	394	29	23	4	0
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	57	4		1	1	56	1	2	2	5
Non-respiratory		0		0	0		1	1	0	0
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	326	33	37	4	6	285	21	27	8	12
Deaths (excluding stillbirths)	9,480	755	530	116	135	8,414	650	534	114	148
LIVE BIRTHS	15,833	1317	1136	301	354	14,274	1200	997	297	346
STILLBIRTHS	309	32	23			281	18	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Rockefeller Foundation Grants

During the third quarter of 1960 Rockefeller Foundation grants totalled $2,167,491, of which $1,155,400 went to the medical and natural sciences.

About $213,750 goes to the University College of Rhodesia and Nyasaland to support a five-year plan of research on human and animal diseases of economic importance in Africa, and, in particular, on sleeping sickness and bilharziasis. A five-year grant of $43,500 has been made for research in human genetics, directed by Professor L. S. Penrose, at University College, London; and a two-year grant of about $20,000 for research in human biochemical genetics, under Professor H. Harris, King's College, London. Professor P. B. B. Gatenby has been granted $1,200 to observe procedures in medical education and the organization of medical teaching at medical schools in the U.S.A., and Professor D. S. Bertram $2,500 to observe research on insect-borne diseases at centres of medical entomology in Egypt, India, Pakistan, and Ceylon. The following have been granted Fellowships for study in the U.S.A.: Dr. D. N. Baron, Dr. C. J. Dickinson, Dr. E. W. Poole, and Dr. P. H. Wright.

Wellcome Research Laboratory, Glasgow University

The Wellcome Research Laboratory, Glasgow University, was formally inaugurated by Sir Henry Dale, O.M., F.R.S., on October 4. Built and to a considerable extent equipped from funds provided by the Wellcome Trust, it will provide facilities for research in human and veterinary medicine.

Sir Henry Dale described the conception of the Wellcome Trust, the dream child of the late Henry Wellcome, and the terms of reference of the Trust which he had caused to be set up. He continued, "I do not think that it could be suggested that the discretion of the trustees was unduly restricted by this detailed indication of the kinds of research which the testator himself, mind you, with no pretensions to being a scientific expert, had nevertheless in his mind for them to support." Sir Henry praised particularly the facilities created in the newly opened laboratories for research jointly conducted by investigators in human and veterinary medicine, possibly for the first time on a deliberately organized basis in this country. He recalled the valuable results of earlier exercises in "reciprocal fertilization of ideas" in the early days of virology, when teams working on projects sponsored by the National Institute for Medical Research and later the Medical Research Council, almost fortuitously using the ferret as host animal, succeeded in isolating in time the virus of canine distemper and then that of human influenza. Sir Henry concluded by saying that he was particularly glad that the new building now being formally opened had begun to be used before he himself recently retired from the chair of the Wellcome Trust. Professor W. L. Weipers, professor of veterinary surgery and director of the veterinary hospital and school, made an appropriate reply.

International Federation of Surgical Colleges

The International Federation of Surgical Colleges met in London, at the Royal College of Surgeons, on October 18 to 20 under the presidency of Sir Harry Platt. The Federation was honoured by a visit from the Duke of Edinburgh. The theme of the meeting was "The Training of Surgeons" (see p. 1305).

The Federation's member institutions at present number 24, and represent 20 countries, the Swiss Surgical Society and Philippine College of Surgeons having recently entered into membership. In March the Federation was admitted into official relations, with consultative status, with the World Health Organization. The Federation, conceived in Chicago in 1955, and born in Stockholm in 1958, has as its objects the improvement and maintenance of standards of surgery throughout the world; the maintenance of close relations among approved surgical colleges and institutions; the maintenance of high standards of education, training, and research; the unification of surgery in all its specialties; support of the clinical and scientific congresses of appropriate surgical organizations; and the promotion of peace in the world by its contribution to understanding among the surgeons of all nations. At a meeting in Munich in 1959 working parties were appointed to examine the problems of surgical missions; training of surgeons; surgical research; and the interchange of young surgeons. Mr. Enoch Powell, the Minister of Health, was the chief guest at a dinner of the Federation at the Royal College of Surgeons on October 19, at which Sir Harry Platt presided. After dinner Sir Arthur Porritt, F.R.C.S., conferred honorary fellowships of the Royal College of Surgeons of England on Professor E. Dahl-Iversen, of Copenhagen, and Professor J. F. Nuboer, of Utrecht. Professor Dahl-Iversen was presented by Professor Ian Aird, and Professor Nuboer by Professor Digby Chamberlain.

Leverhulme Research Awards

Application is invited for Leverhulme Fellowships and grants in aid of research. These awards are intended for senior workers of established position and are limited to British-born subjects normally resident in the United Kingdom; in exceptional circumstances the trustees may waive the condition as to residence. Any subject of inquiry will be considered, but preference is given to those in which existing provision for research is inadequate. Details and application forms may be obtained from the Secretary, Leverhulme Research Awards, St. Bridget's House, Bridewell Place, London E.C.4. The closing date is December 31. Results will be announced in May and the awards will normally date from September 1, 1961.

Talking Book Library for the Blind

The Nuffield Foundation has made a gift of £100,000 to the Nuffield Talking Book Library for the Blind which will enable it to complete its change-over from long-playing records to tape recordings.

The introduction of the new tape play-back machine, illustrated here, was announced recently at the annual meeting of the Royal National Institute for the Blind. It follows almost 25 years of research by the R.N.I.B. and St. Dunstan's. The library lends talking books to over 6,500 blind and often bedridden people, and the circulation figure for the last financial year was well over two million individual disks.

Irish Cardiac Society Presentation

On October 18 the Irish Cardiac Society held a dinner in the Shelbourne Hotel, Dublin, in honour of Dr. P. T. O'Farrell on the occasion of his retirement from practice. He was presented with a silver salver inscribed with the names of the members. Dr. O'Farrell is a Vice-president of the B.M.A. and a Past President.

Electron Microscopy Unit, St. Thomas's Hospital

An electron microscopy unit, provided by the Empire Rheumatism Council at a cost of over £12,000, was recently opened at St. Thomas's Hospital Medical School by Lord Astor of Hever. It will be used for research into rheumatism, with particular reference to cartilage and the part it plays in osteoarthritis. The director of the unit is Professor D. V. Davies, professor of anatomy at the school.

Family Doctor

The November issue of *Family Doctor* is now available, price 1s. 6d. It includes articles by Dr. J. A. C. Brown on "Suburban Neurosis"; by Mr. Randell Champion on "Burning Accidents"; by Mr. D. Le Vay on "Knock-knees and Bow-legs"; and by Mr. R. Scott Stevenson on "Catarrh."

In Brief

Membership of the Royal College of Nursing will be open to all registered nurses of either sex from November 1.

People in the News

Dr. N. Malleson has been appointed director of the new research unit for student problems at the University of London Institute of Education. The unit will undertake and foster sociological and operational research into problems of student performance and student life in the University generally.

"The Inter-relationships of the Collagen Disorders."

Dr. J. J. Bunim (National Institute of Health, Bethesda, Maryland, U.S.A.), who is delivering the Heberden Oration, will lecture on this subject in the Meyerstein Theatre, Westminster Medical School, on November 30, 5.30 p.m.

COMING EVENTS

Institute of Dermatology, London. — Exhibition, November 7 to 30, Dr. P. D. Samman, "Cutaneous Tuberculosis and Sarcoidosis."

B.M.A. (Glasgow and West of Scotland Branch) Glasgow Division.—Four closed-circuit colour television demonstrations, by arrangement with Messrs. Smith Kline and French Laboratories, Ltd.: November 8, 3.30 p.m., "The Diagnosis of Lumps"; November 9, 3.30 p.m., "Transventricular Mitral Commissurotomy"; 8.30 p.m., "Painful Syndromes of the Upper Limb"; November 10, 8.30 p.m., "Hiatus Hernia." At McLellan Galleries, Glasgow.

1st Cecil Gordon Memorial Lecture.—Professor Lancelot Hogben, F.R.S., "The Nature–Nurture Issue and the Medical Curriculum," West Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, November 10, 5 p.m.

Association of School Medical and Dental Officers of Scotland.—Meeting, Western General Hospital, Edinburgh, November 12, 10.30 a.m. Speakers: Dr. W. M. Court Brown, "Recent Advances in Human Cytogenetics (with Particular Reference to the Leukaemias)." Miss P. A. Jacobs, B.Sc., "Aberrations of Sex Chromosomes and their Implication in the Determining of Mongolism and Other Forms of Mental Defect." Dr. Maud P. Menzies, Honorary Secretary, Rosmaris, 34 Rhannan Road, Glasgow S.4.

London Medical Exhibition.—November 14–18, Horticultural Hall, Greycoat Street, Westminster, London S.W.1.

B.B.C. Television.—"The Vintage Years," a series on the problems of old age: (1) November 17, Preparation for retirement, both practical and psychological. (2) November 24: What it feels like to be old; how old people live. (3) December 1: Aids for the aged. (4) December 8: Illness in old age, with reference to such new developments as day hospitals; the extent to which people can come to terms with old age.

St. Mark's Hospital.—Conference, in association with the British Postgraduate Medical Federation, for consultant surgeons on diseases of the colon and rectum, St. Mark's Hospital, City Road, London E.C.1, November 18, 19. Details from the Dean of Postgraduate Studies at the hospital.

Bethlem Royal and Maudsley Hospitals.—Medical staff ball for past and present members, Kensington Palace Hotel, November 18. Double tickets (3 guineas each) from Dr. B. Ackner, the Maudsley Hospital, Denmark Hill, London S.E.5.

35th Maudsley Lecture, Royal Medico-Psychological Association.—Dr. Eliot Slater, "Hysteria 311," November 18, 2.15 p.m., Royal Society of Medicine, Barnes Hall, 1 Wimpole Street, London W.1. Admission without ticket.

Faculty of Radiologists.—Postgraduate week-end course on diagnostic radiology and radiotherapy, November 19, 20, at the Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2. Details from the Secretary of the Faculty of Radiologists, at that address. (Tel. HOLborn 3474.)

Hand Club and Second-Hand Club.—Open meeting, Royal College of Surgeons, London, 10 a.m., November 19. Papers welcomed from non-members. Details from Mr. H. Graham Stack, 150 Harley Street, London W.1.

St. John's Hospital, Chelmsford.—Postgraduate courses for general practitioners in practical and theoretical obstetrics and gynaecology are being held at the hospital throughout the year. Details from Mr. David Brown, St. John's Hospital, Wood Street, Chelmsford, Essex.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

THORAX

Experience with Perfusion Hypothermia Using an Improved Rotating Disc Oxygenator. Frank Gerbode, John J. Osborn, and J. Bruce Johnston.
Clinical Experience with the Melrose Oxygenator at Normal and Reduced Temperatures. P. G. F. Nixon, V. A. Grimshaw, L. A. Catchpole, H. M. Snow, and K. Lawrance.
Fatal Nephritis Complicating Idiopathic Pulmonary Haemosiderosis in Young Adults. Catherine S. MacGregor, R. Sleigh Johnson, and K. A. D. Turk.
A Report of 12 Selected Cases of Pulmonary Histoplasmosis. Alex Saliba and Oren A. Beatty.
A Syndrome Resembling Farmer's Lung in Workers Inhaling Spores of Aspergillus and Penicillin Moulds. Miloš Hořejší, Josef Šach, Alena Tomšíková, Antonín Mecl, Dana Blahníková, Milada Tůmová, and Anežka Vališová.
Transection Operations for Portal Hypertension. R. Milnes Walker.
The Transeptal Approach to Left Atrium in Mitral Regurgitation. P. G. F. Nixon.
Anatomical Observations on the Course of the Azygos Vein (Vena Azygos Major). Hilel Nathan.
The Conservative Treatment of the Tension Lesions of Staphylococcal Pneumonia in Infancy. James S. Davidson.
Observations on 100 Cases of Bronchial Carcinoma in a Rural Area. B. R. Hillis and J. A. Cameron.
Respiratory Function and Portable Oxygen Therapy in Chronic Non-specific Lung Disease in Relation to Prognosis. J. E. Cotes.
The Malignant Solitary Pulmonary Lesion. Pekka Tala and Lauri Virkkula.
A Case of Cytomegalic Inclusion Disease. T. M. Vanier.
Respiratory Crisis After Thymectomy in Patients with Myasthenia Gravis. George W. Pennington and F. Ronald Edwards.
Aneurysm of an Intercostal Artery After Paracentesis Thoracis. J. S. Elkington and J. B. L. Howell.
Preparation and Assembly of the Stainless Steel Sponge Debubbler for Use in the Helix Reservoir Bubble Oxygenator. C. N. Barnard, M. B. McKenzie, and Dr. R. de Villiers.

Volume 15, No. 3. (Quarterly; £3 annually.)

JOURNAL OF CLINICAL PATHOLOGY

Radioactive Isotopes in Medicine: A Review. C. J. Hayter.
Short-term Assessment of Red Blood Cell Survival Using ^{51}Cr. N. F. Jones, G. Wetherley-Mein, G. I. C. Ingram, and W. A. Langmead.
The Absorption of Vitamin B_{12} in Megaloblastic Anaemia Associated with Pregnancy. J. Metz, S. M. Lewis, K. J. Keeley, and D. Hart.
Tissue Reactions to Aspergillus in Cases of Hodgkin's Disease and Leukaemia. N. F. C. Gowing and Iris M. E. Hamlin.
The Differential Diagnosis of Tumour Cells in Circulating Blood. R. F. Alexander and A. I. Spriggs.
The Diagnostic Value of Pleural Biopsy in Bronchopulmonary Carcinoma. Walter Pagel and Susan Goldfarb.
Three Cases of Acute Mesenteric Lymphadenitis Due to Pasteurella Pseudotuberculosis. N. S. Mair, Hélène J. Mair, E. M. Stirk, and J. G. Corson.
Folic Acid and Other Absorption Tests in Lymphosarcoma, Chronic Lymphocytic Leukaemia, and Some Related Conditions. W. R. Pitney, R. A. Joske, and Norma L. Mackinnon.
Anti-gamma-globulin Consumption Test in Hashimoto's Disease. E. J. Field and A. Ridley.
Studies on Reanimation with Plasma Expanders. C. T. Nicolau, Cecil Poppa, M. Ialomiteanu, R. Pîrvu, and M. Ionescu.
The Latex Slide Test in Rheumatic Disorders. J. V. Wilson, R. A. H. Morison, and V. Wright.
Book Reviews.

Volume 13, No. 5. (Bi-monthly; £4 4s. annually.)

ARCHIVES OF DISEASE IN CHILDHOOD

Spinal Dysraphism. C. C. Michael James and L. P. Lassman.
Cortical Atrophy of the Brain in Infants Associated with Failure to Thrive. P. M. Smythe and I. A. D. Bouchier.
The Incidence of Twins in Cerebral Palsy and Mental Retardation. R. S. Illingworth and Grace E. Woods.
Convulsive Movements Occurring in the First Ten Days of Life. W. S. Craig.
Familial Diffuse Progressive Encephalopathy. M. C. Liu and Peter E. Sylvester.
Postnatal Plasma Shift in Premature Infants. A. C. L. Clark and Douglas Gairdner.
Absorption of Radioactive Iron by Anaemic Infants. Ian D. Riley.
Haemoglobin "Barts"—A Rare Abnormality in the Newborn. Dorothy H. E. Barrow and H. G. Kohler.
Systemic Lupus Erythematosus in Pregnancy with Haemolytic Anaemia, Leucopenia and Thrombocytopenia in the Mother and her Newborn Infant. Martin Seip.
Pancytopenia with Congenital Defects (Fanconi's Anaemia). Robert McDonald and Basil Goldschmidt.
Studies in Hirschsprung's Disease. J. R. Trounce and A. Nightingale.
Spontaneous Perforation of the Colon in the Newborn Infant. S. E. Levin and C. Isaacson.
The Prognosis in Idiopathic Hypercalcaemia of Infants. R. G. Mitchell.
Pneumomediastinum and Subcutaneous Emphysema in Status Asthmaticus, Requiring Surgical Decompression. Brian McNicholl.
Creatinuria in Möbius' Syndrome. Patricia G. Wallis.
Prostatic Abscess in the Newborn. Stewart Mann.
Iliac Vein Obstruction Due to a Retroperitoneal Abscess. P. J. Lipsitz.
The Diagnosis and Treatment of Hermaphroditism. C. C. Winkel Smith.
British Paediatric Association: Proceedings of the Thirty-first Annual General Meeting.
Book Reviews.

Volume 35, No. 182. (Bi-monthly; £4 4s. annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 31

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Mr. G. W. Garland: Antenatal Supervision.

POSTGRADUATE MEDICAL SCHOOL.—4 p.m., Dr. W. Sircus: Practical Application of Gastric Secretion Studies.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. J. S. S. Stewart: Surgical Aspects of Genetics.

Tuesday, November 1

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor M. Stoker: Latent Virus Infections.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. D. Porter: Keratinization, Normal and Abnormal.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. W. Ritchie Russell: Neurological Aspects of Memory.

LONDON UNIVERSITY.—At Middlesex Hospital Medical School, 5.15 p.m., special university lecture in physiology by Professor Hans Schaefer (Heidelberg): Principles of Circulatory Regulation.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arris and Gale Lecture by Mr. N. H. Porter: Physiological Study of the Pelvic Floor Muscles in Rectal Prolapse.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Dr. Elliot Philipp: Antepartum Haemorrhage.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. H. C. Grant: Chronic Meningitis.

Wednesday, November 2

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Mr. R. E. Beard, F.I.A.: Some Thoughts on Mortality, Morbidity, and Medical Underwriting.

BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY SECTION.—At 36 Harborne Road, Edgbaston, 8.30 p.m., joint meeting with Midland Counties Veterinary Association. Dr. J. D. Rankin and Dr. K. B. Rogers: Diseases of Animals Communicable to Man.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Tickner: Biochemistry of Pigmentation.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. W. D. W. Brooks: Spontaneous Pneumothorax.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. J. D. Fergusson: Cancer of the Prostate.

●LEEDS UNIVERSITY.—At General Infirmary at Leeds, (1) 5 p.m., Mr. D. W. Currie: Cancer of the Female Genital Tract. (2) 6 p.m., Mr. H. Agar: General Surgical Problems in Gynaecology.

LONDON AMATEUR BOXING ASSOCIATION.—At British Railways Film Unit, Savile Row, W., 8 p.m., meeting of Medical Advisory Panel, London A.B.A., Dr. J. L. Blonstein: Olympic Games in Retrospect.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Charles Wilcocks: Aspects of Medical Investigation in Africa—Tuberculosis.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., Dr. C. J. Hodson: Radiological Observations on the Natural History of Chronic Pyelonephritis.

POSTGRADUATE MEDICAL SCHOOL.—2 p.m., Professor R. H. S. Thompson: Biochemistry of Multiple Sclerosis.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. J. B. Enticknap: Coronary Thrombosis and Other Forms of Ischaemic Heart Disease.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.—5.15 p.m., special lecture by Dr. F. J. W. Miller: Thousand Families Survey.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. F. Ward: Flammability of Textile.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Dr. W. W. Park: Embolism Within the Pulmonary Circulation.

Thursday, November 3

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. K. M. Rudall: Regular Folds in Protein and Polysaccharide Chains.

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor J. H. Kellgren: Osteoarthrosis in Patients and Populations.

INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. Catherine Hebb: Intracellular Structures and Transmitter Substances in the Nervous System.

LIVERPOOL MEDICAL INSTITUTION.—Florence Blair-Bell Memorial Lecture by Mr. Ronald W. Raven.

LONDON UNIVERSITY.—(1) At Royal Society of Medicine, 5 p.m., Semon Lecture by Professor Paul H. Holinger (Illinois): Clinical Aspects of Congenital Anomalies of the Larynx, Trachea, Bronchi, and Oesophagus. (2) At Middlesex Hospital Medical School, 5.15 p.m., special university lecture in physiology by Professor Hans Schaefer (Heidelberg): Theory and Interpretation of the Electrocardiogram. (3) At London School of Hygiene and Tropical Medicine 5.30 p.m., Heath Clark Lecture by Dr. Charles Wilcocks: Aspects of Medical Investigation in Africa—Schistosomiasis.

NORTH-WESTERN THORACIC SOCIETY.—At Aintree Hospital, Liverpool, 5 p.m., Dr. J. Howell: Physiological Aspects of CO_2 Retention; Dr. C. Ogilvie: Clinical Aspects of CO_2 Retention.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Mr. H. V. Crock: Experiments on Spinal Fusion in the Dog.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Bradshaw Lecture by Dr. W. I. Card: Concept of Gastric Secretory Cell Mass.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. M. A. Partridge: postgraduate demonstration in psychiatry.

Friday, November 4

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. S. C. Gold: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. D. Barlow: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—(1) 12 noon, Dr. Paul Holinger (Chicago): Endoscopy in Otolaryngic Pathology (2) 3.30 p.m., clinical discussion for general practitioners. Dr. I. Friedmann: Advances in Chemotherapy.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 3 p.m., Professor E. C. Amoroso: Endocrinology of Pregnancy.

MEDICAL ELECTRONICS DISCUSSION GROUP.—At Institution of Electrical Engineers, Savoy Place, London, W.C., 5.30 for 6 p.m., discussion to be opened by Dr. A. Spencer Paterson and Mr. W. H. Stanton: Electroconvulsive Therapy.

PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., Mr. G. L. Alexander: Danger Signs in Cases of Head Injury.

POSTGRADUATE MEDICAL SCHOOL.—(1) 10 a.m., Mr. K. C. McKeown: Gastrectomy in Peptic Ulcer. (2) 4 p.m., Dr. B. E. C. Nordin: Osteomalacia and Osteoporosis.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. G. P. T. Barclay: Recent Studies of the Myocardium.

Sunday, November 6

UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main Hospital. Lecture demonstration for general practitioner, Professor A. S. Prophet, D.D.S., Dip.Bact., F.D.S. R.C.S.: Dental Emergencies in General Practice.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—S. J. Raverty, L.R.C.P.&S.I., L.M., Registrar in Psychiatry, Suffolk Mental Hospitals; G. A. Chaudhary, M.B., B.S., Registrar in Geriatrics, West Suffolk Hospital Group; R. G. Huntsman, M.B., B.Chir., M.R.C.P., Consultant Pathologist, Peterborough, Wisbech and King's Lynn Areas; S. K. Kapur, M.B., B.S., D.T.M.&H., Medical Registrar, Papworth Hospital; R. G. B. Turner, M.B., Ch.B., Registrar in Plastic Surgery, Regional Burns and Plastic Surgery Unit, West Norwich Hospital.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—D. F. Gibbs, M.B., Ch.B., M.R.C.P.Ed., Assistant Geriatrician (S.H.M.O.) to Devon and Exeter Clinical Area; G. Vine Cole, M.R.C.S., L.R.C.P., D.O., Ophthalmologist (S.H.M.O.) to Plymouth Clinical Area; B. Philpott, M.B., B.S., D.A., Anaesthetic Registrar, Frenchay Hospital, Bristol; C. P. Gyaw, M.B., B.S., D.A., Anaesthetic Registrar, H. A. McClelland, M.B., B.S., D.C.H., D.Obst.R.C.O.G., Medical Registrar, and N. L. Browse, M.B., B.S., F.R.C.S., Surgical Registrar, all to Southmead Hospital, Bristol; J. E. Trapnell, M.B., B.Chir., Surgical Registrar, Cossham-Frenchay Group of Hospitals, Bristol; J. R. Burgess, M.R.C.S., L.R.C.P., and R. A. Flood, M.B., Ch.B., D.P.M. (reappointed), Registrars in Psychiatry, Bristol Mental Group of Hospitals; J. C. Anderson, M.Ch.Orth., F.R.C.S.Ed., Senior Registrar in Orthopaedic and Traumatic Surgery, S. K. H. Zaidi, M.B., B.S., Anaesthetic Registrar, and J. W. Crawford, M.B., Ch.B., D.Obst. R.C.O.G., Registrar in Obstetrics and Gynaecology, all to the Bath Group of Hospitals; W. H. Cadzow, M.B., B.S., Surgical Registrar, and M. F. Holding, M.B., B.Ch., D.Obst.R.C.O.G., Medical Registrar, both to Gloucestershire Royal Hospital, Gloucester; P. C. Foley, M.B., B.Ch., Medical Registrar, Cheltenham General Hospital; S. T. Whitehead, M.B., Ch.B., Surgical Registrar, Torbay/Newton Abbot Hospitals; W. F. W. Southwood, M.Chir., F.R.C.S., Senior Surgical Registrar, and Gillian A. Jefferies, M.B., B.S., D.A., Anaesthetic Registrar, both to Royal Devon and Exeter Hospital; J. F. Cam, M.B., B.S., Anaesthetic Registrar, and J. P. Coutts, M.B., Ch.B., F.R.C.S., Surgical Registrar, both to South Devon and East Cornwall Hospital, Plymouth; M. C. Moss, M.B., B.S., D.P.M., Senior Registrar in Psychiatry, Moorhaven Hospital, Plymouth; I. F. Anderson, M.B., B.S., Registrar in Obstetrics and Gynaecology, Camborne-Redruth Hospital, Cornwall.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Armatage.—On September 21, 1960, at the Norfolk and Norwich Hospital, to Dr. and Mrs. Robin Armatage, of Sheringwood, Loddon, Norfolk, a daughter—Susan Elizabeth.

Roe.—On Monday October 10, 1960, at Edgware General Hospital, Edgware, Middx, to Kathleen, wife of Dr. Peter Watney Roe, a daughter—Catherine Margaret.

MARRIAGES

Bagnall—Tucker.—On September 22, 1960, at Broadwater Parish Church, Worthing, Sussex, Kenneth Winfield Bagnall, D.Sc., F.R.I.C., to Joyce Ferry Tucker, M.D., M.R.C.P., D.C.H.

DEATHS

Aberdein.—On September 29, 1960, Alexander Aberdein, M.B., Ch.B., of Overwoods, Little Aston Park, Sutton Coldfield.

Brown.—On October 3, 1960, John Clifford Brown, M.R.C.S., L.R.C.P., Surgeon Captain, R.N., retired, of Exmouth, Devon.

Cimbelmann.—On September 29, 1960, in St. Bartholomew's Hospital, London E.C., Benjamin Cimbelmann, M.D., of 7 Garson House, Gloucester Terrace, London W., aged 59.

Davies.—On October 2, 1960, at Withybush Hospital, Haverfordwest, Pembs, Rowland Selby Gwyn Davies, M.B., Ch.B., of Trecwn, Pembs, and Treforfan, Fishguard, Pembs, aged 39.

Evans.—On October 4, 1960, in hospital, William Burnett Evans, T.D., M.D., of Milford Haven, Pembs, aged 53.

Johnson.—On October 5, 1960, at Wooler, Northumberland, John Tyrer Johnson, D.S.O., M.D., D.P.H., Colonel, R.A.M.C., retired.

Lee.—On September 29, 1960, at his home, 36 York Street, Sandy Bay, Hobart, Tasmania, Harrie Bertie Lee, D.S.O., *M.C.* M.B., B.S., D.T.M.&H., formerly of Medical Service, Nigeria, aged 72.

Lees.—On October 3, 1960, in a nursing-home, Worthing, Sussex, Bernard Hall Lees, M.B., B.Ch., aged 92.

MacKay.—On September 30, 1960, Rachel Brodie MacKay, M.D., of 4 Coates Place, Edinburgh.

Roberts.—On September 27, 1960, John William Nelson Roberts, L.R.C.P.&S.Ed., L.R.F.P.S., of Talarvor, Criccieth, Caern.

Somerset.—On October 5, 1960, at his home, Oakfield, Crofts Bank Road, Urmston, Lancs, Robert Masters Somerset, M.R.C.S., L.R.C.P.

Tate.—On October 5, 1960, at 370 Ormeau Road, Belfast, James Tate, M.B., B.Ch., M.R.C.P., D.P.H.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Anaemia in Pregnancy

Q.—*What should be the treatment for pregnant women who, despite oral iron during the previous months, have only 60% to 70% Hb at the 34th week ?*

A.—The problem presented by this question can be generally prevented by giving pregnant women folic acid as well as iron by mouth. This is especially important during the last 12 weeks of pregnancy. Many cases of supposed iron-deficiency anaemia in association with pregnancy are unrecognized cases of megaloblastic anaemia. Not only does the routine administration of folic acid (5 mg. three times a day by mouth) prevent the appearance of established megaloblastic anaemia in late pregnancy, but, given in conjunction with iron, it seems to help in the prevention or cure of anaemias of a less clearly defined nature. In this respect ascorbic acid in a dose of 50–100 mg. daily may also help by assisting the absorption of iron or by activating folic acid. A controlled study showing the value of this sort of routine treatment during pregnancy was reported by C. Giles and H. Burton.[1]

If the patient in question is already 34 weeks pregnant, the administration of folic acid in addition to iron may still produce a dramatic response. Failing such, special preparations of iron can be given intravenously daily or on alternate days in doses of 100 mg. The initial dose should be small to test for undesirable reactions and the total dose should not exceed 1,000 mg. The maximum effect is not seen for 14–21 days after the course is begun.

If significant anaemia (haemoglobin below 70%) is present as term approaches then it becomes necessary to prepare the patient for safe labour by transfusing blood.

REFERENCE

[1] Giles, C., and Burton, H., *Brit. med. J.*, 1960, **2**, 636.

Blood Culture

Q.—*What is the technique of blood culture in the investigation of pyrexia of undiagnosed cause? What number and types of media are used and in what quantity in each flask? What should be the size of the inoculum and for how many days should it be incubated ?*

A.—The requirements for successful blood culture are: (1) Neutralization of the bactericidal power of the blood, which otherwise may sometimes destroy the bacteria contained in it. "Liquoid" (sodium polyanethol sulphonate) is best for this: it may be included in the culture medium in a concentration not exceeding 0.05%. Alternatively, since it is also an anticoagulant, it may be used initially for this purpose also: 0.5 ml. of a 0.5% solution (sterilized by autoclaving) is enough for 10 ml. of blood. (2) Suitable culture media. A good nutrient broth serves most purposes; other factors sometimes necessary for growth are provided by the blood itself. Of other media indicated for special purposes a broth containing bile salt (e.g., 1% sodium taurocholate), or simple ox bile enriched with 1% peptone, accelerates the growth of organisms of the enteric group. (3) Suitable atmospheric conditions. When the diagnosis is in doubt, separate cultures should be incubated aerobically, anaerobically, and in 5% CO_2.

The media used may be in tubes, flasks or bottles: both the total volume and the relative volumes of medium and blood are indifferent within fairly wide limits if liquoid is used and provided that an adequate total volume of blood is cultivated, but a proportion of about 1 part of blood to 4 of medium is convenient. If pour plates are also made in nutrient agar (colonies can often be seen in these before growth is visible in liquid cultures, particularly in cases of bacterial endocarditis) 0.5 or 1 ml. of blood may be added to a tube of medium (±15 ml.) which has been melted and cooled to 47° C.

Growth usually appears in two days, but no cultures should be discarded before the seventh day, and, if brucellosis is suspected, before the 14th.

Oxygen Insufflation and Respiratory Alkalosis

Q.—*When an apnoeic patient is oxygenated by the insufflation of a high-flow rate of air or oxygen pertracheally is there tendency towards (1) respiratory alkalosis, or (2) respiratory acidosis ?*

A.—It has been known for some time[1] that an apnoeic patient from whom most of the nitrogen in the blood has been extracted will remain oxygenated for at least half an hour, so long as the trachea and bronchi are filled with oxygen and are connected to a bag filled with oxygen. However, in these circumstances, considerable carbon dioxide retention occurs; in fact, it is the difference between the volume of carbon dioxide leaving the blood and the volume of oxygen entering it that gives rise to the lowered alveolar pressure and hence the flow of oxygen from the air passages in the alveoli.[2] In human subjects the pCO_2 in the arterial blood has been found to rise at the rate of about 3–4 mm. Hg per minute. The insufflation of oxygen into the trachea can remove carbon dioxide only from the region of the catheter end. Respiratory acidosis still occurs. In one report,[3] when 3 litres per minute were insufflated the *p*H fell to 6.97 and pCO_2 rose to 115 mm. Hg at the end of 30 minutes. Other reports[4] confirm the tendency for acidosis to occur in these circumstances. It is doubtful if respiratory acidosis in apnoeic patients could be prevented with flows and catheters within practical limits. In any case the high intrapulmonary pressure so produced might lead to other serious side-effects.

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[1] Draper, W. B., and Whitehead, R. W., *Anesth. Analg. Curr. Res.*, 1949, **28**, 307.
[2] Frumin, M. J., Epstein, R. M., and Cohen, G., *Anesthesiology*, 1959, **20**, 789.
[3] Jooste, K. H., *Anaesthesia*, 1955, **10**, 59.
[4] Cneatle, C. A., and Chambers, K. B., Ibid., 1955, **10**, 171.

Reiter's Syndrome

Q.—*A young man presented with non-gonococcal urethral discharge, slightly swollen inguinal glands, followed by pain and rubor in wrists, fingers, knees, and ankles and associated conjunctivitis. What is the best form of treatment ? How often can one expect relapses and if they do occur can they be treated in the same way as the original attack ?*

A.—Presumably this is a case of the triple syndrome of non-gonococcal urethritis, polyarthritis, and conjunctivitis, sometimes called Reiter's disease or Reiter's syndrome.

The patient requires strict bed rest, good nursing, and good feeding. Admission to hospital is usually desirable. None of the antibiotics at present available influences the course of the arthritis, but tetracycline 250 mg. may be given every six hours for five days and has a favourable effect on the urogenital infection in many cases. In mild cases calcium aspirin may suffice for the relief of pain, but in more severe cases phenylbutazone 200 mg. given twice or three times daily often gives striking relief. Steroid hormones should be reserved for severe cases treated in hospital. When the active phase of the arthritis is subsiding the patient should be mobilized and gentle active physiotherapy should be begun. The associated conjunctivitis is usually mild and does not generally require treatment.

The condition is prone to relapse, but weeks, months, or years may intervene between individual attacks. It seems probable that later attacks are sometimes determined by reinfection from a sexual partner. Such partners should

always be investigated and treated if necessary. Individual attacks may last anything from a few weeks to many months. Recurring attacks may be treated in the manner described, but recurrence carries with it the risk of developing anterior uveitis, which requires skilled management by an ophthalmologist for a period of months or years.

Chemotherapy in Meningitis

Q.—*Would you please outline the best routine chemotherapy for (1) pneumococcal and (2) haemophilus meningitis?*

A.—(1) If large doses of penicillin are given by intramuscular injection to patients with pneumococcal meningitis a satisfactory C.S.F. level of the antibiotic can be obtained and intrathecal injection of penicillin is not usually needed. The dosage recommended is a mega unit of penicillin every two hours. Penicillin and chlortetracycline should not be given together to such patients, as these two antibiotics are antagonistic. Some clinicians, however, consider that intrathecal penicillin should be administered in addition to large doses of intramuscular penicillin and give 10,000 units by lumbar puncture daily for the first three to four days of treatment.

(2) Chloramphenicol orally is considered to be the antibiotic of choice in haemophilus meningitis, but good results have also been reported from the combined use of intramuscular streptomycin, intrathecal streptomycin, and oral sulphadiazine—for example, McKendrick[1] reported only one death in a series of 17 cases treated in this way.

Reference

1 McKendrick, G. D. W., *Lancet*, 1954, 2, 510.

Muscle-relaxants and Arthritis

Q.—*Muscle-relaxants are now prescribed in some cases of osteoarthritis of the hip. Presumably this relieves pain due to muscle spasm and facilitates walking, but how does this fit in with the observation that muscle wasting and weakness occur in this condition, and that unsteadiness of the joint gives rise to pain and renders the joint liable to further trauma?*

A.—The point made in the question is a very good one. Most of the so-called muscle spasms which occur in the rheumatic disorders are, in fact, a voluntary contraction in response to sudden pain in the affected joint. This is a protective mechanism, and were the muscle-relaxants used one hundred per cent. effective the pains in these cases would probably be very much worse and the relaxants given up by the patient. The word "spasm" is loosely used in osteoarthritis of the hip. One gets involuntary spasmodic contractions, which are extremely painful. These contractions (or spasms) can take place in the face of a good deal of stiffness and muscle wasting. Effective analgesics are, on the whole, more effective therapy, since they allow more normal function and more normal use of the joint and muscles.

Pharmacological Castration

Q.—*What dose of stilboestrol or ethinyl oestradiol is required for pharmacological castration of a young or middle-aged male (1) initially, and (2) for maintenance? Apart from mammary hyperplasia and testicular atrophy, could alteration in the voice, growth of hair, distribution of body fat, etc., be expected? Finally, if the patient continued with the drug over a long period, is there any reason to suppose it might be carcinogenic or produce ill-effects other than those desired.*

A.—A daily dose of stilboestrol 2 mg. or ethinyl oestradiol 0.1 mg. would probably be quite sufficient to produce pharmacological castration. A larger initial dosage might be more rapidly effective but would be likely to cause nausea or other "side-effects."

Voice changes would not be expected, but the growth of the beard would decrease, the scalp hair would become finer and more silky, and the skin generally smoother and less greasy. Fat accumulation around the hips would possibly occur. The temperament would probably become more placid but there might be depression.

Carcinogenesis from long-term uninterrupted oestrogen therapy cannot be dismissed as a merely theoretical possibility, though the clinical evidence for it is not convincing. If the patient is young rather than middle aged, surgical castration might be preferable to indefinitely continued oestrogen treatment.

Giardia Intestinalis

Q.—*Are there any recent advances in the treatment of Giardia intestinalis infestation apart from mepacrine?*

A.—The standard and most effective remedy available for infection with *Giardia intestinalis* continues to be mepacrine. The usual adult dosage is 100 mg. thrice daily for 6–8 days.

NOTES AND COMMENTS

Streptomycin in Acute Pancreatitis.—Mr. Rodney Smith (London W.1) writes: The answer to your correspondent relating to the treatment of acute pancreatitis ("Any Questions?" October 1, p. 1032) contains what must surely be a record number of statements long shown to be untrue. It is now universally agreed that morphine should *not* be given. It is unlikely to be effective and may very well be harmful. All authorities agree that plasma (or whole blood) is of value, particularly in the more severe cases, but when indicated the suggested 250–500 ml. is totally inadequate. Gastric suction should not be advised "if ileus develops." It should be used in every case, not only in order to anticipate and prevent dilatation of the stomach and small bowel but also to reduce pancreatic secretion by withdrawing the stimulus of gastric contents entering the duodenum. The most dangerous statement of all is that "Surgical intervention is almost always required to confirm the diagnosis. . . ." This is completely untrue. The mortality of acute pancreatitis has decreased markedly during the last decade and probably the most important single factor leading to this has been the general acceptance of the fact that the bad cases must not be submitted to an exploratory laparotomy. The mere fact of exploration decreases the patient's chance of survival, and if, in error, the abdomen has been opened the surgeon will be well advised to close it again as swiftly as possible, for the greater the extent of the surgical interference the more the hazard is increased.

Our Expert replies: These forceful criticisms serve to emphasize the differences in current opinion as to the management of this serious disease. I am glad that my pedestrian remarks have provoked such cogent comment from so distinguished an authority in this field, who has indicated the possible alternatives in the treatment advised.

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